Rochester
2016 Interpretive Handbook

Sorted By Test Name

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Definition of Specimen "Minimum Volume"

Defines the amount of specimen required to perform an assay once, including instrument and container dead space. Submitting the minimum specimen volume makes it impossible to repeat the test or perform confirmatory or perform reflex testing. In some situations, a minimum specimen volume may result in a QNS (quantity not sufficient) result, requiring a second specimen to be collected.
POLICY STATEMENTS

Animal Specimens
We do not accept animal specimens for laboratory testing.

Billing
Client—Each month you will receive an itemized invoice/ statement which will indicate the date of service, patient name, CPT code, test name, and test charge. Payment terms are net 30 days. When making payment, please include our invoice number on your check to ensure proper credit to your account.

Patient—Mayo Medical Laboratories does not routinely bill patient’s insurance; however, if you have made advanced arrangements to have Mayo Medical Laboratories bill your patient’s insurance, please include the following required billing information: responsible party, patient’s name, current address, zip code, phone number, Social Security number, and diagnosis code. Providing this information will avoid additional correspondence to your office at some later date. Please advise your patients that they will receive a bill for laboratory services from Mayo Medical Laboratories for any personal responsibility after insurance payment. VISA® and MasterCard® are acceptable forms of payment.

Billing—CPT Coding
It is your responsibility to determine correct CPT codes to use for billing. While this catalog lists CPT codes in an effort to provide some guidance, CPT codes listed only reflect our interpretation of CPT coding requirements and are not necessarily correct. Particularly, in the case of a test involving several component tests, this catalog attempts to provide a comprehensive list of CPT codes for all of the possible components of the test. Only a subset of component tests may be performed on your specimen. You should verify accuracy of codes listed. Where multiple codes are listed, you should select codes for tests actually performed on your specimen. MAYO MEDICAL LABORATORIES ASSUMES NO RESPONSIBILITY FOR BILLING ERRORS DUE TO RELIANCE ON CPT CODES LISTED IN THIS CATALOG. For further reference, please consult the CPT Coding Manual published by the American Medical Association. If you have any questions regarding use of a code, please contact your local Medicare carrier.

Business Continuity and Contingency Planning
In the event of a local, regional, or national disaster, Mayo Clinic and Mayo Medical Laboratories’ performing sites have comprehensive contingency plans in place in each location to ensure that the impact on laboratory practice is minimized. With test standardization between our performing sites and medical practice locations throughout the country, we have worked to ensure that patient care will not be compromised.

Cancellation of Tests
Cancellations received prior to test setup will be honored at no charge. Requests received following test setup cannot be honored. A report will be issued automatically and charged appropriately.

Chain-of-Custody
Chain-of-custody, a record of disposition of a specimen to document who collected it, who handled it, and who performed the analysis, is necessary when results are to be used in a court of law. Mayo Medical Laboratories has developed packaging and shipping materials that satisfy legal requirements for chain-of-custody. This service is only offered for drug testing.
Compliance Policies
Mayo Medical Laboratories is committed to compliance with applicable laws and regulations such as the Clinical Laboratory Improvement Amendments (CLIA). Regulatory agencies that oversee our compliance include, but are not limited to, the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Department of Transportation (DOT). Mayo Medical Laboratories develops, implements, and maintains policies, processes, and procedures throughout our organization which are designed to meet relevant requirements. We expect clients utilizing our services will ensure their compliance with patient confidentiality, diagnosis coding, anti-kick back statutes, professional courtesy, CPT-4 coding, CLIA proficiency testing, and other similar regulatory requirements. Also see “Accreditation and Licensure,” “HIPAA Compliance,” and “Reportable Disease.”

Confidentiality of Results
Mayo Medical Laboratories is committed to maintaining confidentiality of patient information. To ensure Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the College of American Pathologists (CAP) compliance for appropriate release of patient results, Mayo Medical Laboratories has adopted the following policies:

Phone Inquiry Policy—One of the following unique identifiers will be required:
- Mayo Medical Laboratories’ accession ID number for specimen; or
- Client account number from Mayo Medical Laboratories along with patient name; or
- Client accession ID number interfaced to Mayo Medical Laboratories; or
- Identification by individual that he or she is, in fact, “referring physician” identified on requisition form by Mayo Medical Laboratories’ client

Under federal regulations, we are only authorized to release results to ordering physicians or health care providers responsible for the individual patient’s care. Third parties requesting results including requests directly from the patient are directed to the ordering facility. We appreciate your assistance in helping Mayo Medical Laboratories preserve patient confidentiality. Provision of appropriate identifiers will greatly assist prompt and accurate response to inquiries and reporting.

Critical Values
The “Critical Values Policy” of the Department of Laboratory Medicine and Pathology (DLMP), Mayo Clinic, Rochester, Minnesota is described below. These values apply to Mayo Clinic patients as well as the extramural practice administered through affiliate Mayo Medical Laboratories. Clients should provide “Critical Value” contact information to Mayo Laboratory Inquiry to facilitate call-backs. To facilitate this process, a customized form is available at mayomedicallaboratories.com

Definition of Critical Value—A critical value is defined by Mayo Clinic physicians as a value that represents a pathophysiological state at such variance with normal (expected values) as to be life-threatening unless something is done promptly and for which some corrective action could be taken.

Abnormals are Not Considered Critical Values—Most laboratory tests have established reference ranges, which represent results that are typically seen in a group of healthy individuals. While results outside these reference ranges may be considered abnormal, “abnormal” results and “critical values” are not synonymous. Analytes on the DLMP Critical Values List represent a subgroup of tests that meet the above definition.

Action Taken when a Result is Obtained that Exceeds the Limit Defined by the DLMP Critical Values List—In addition to the normal results reporting (eg, fax, interface), Mayo Medical Laboratories’ staff telephone the ordering physician or the client-provided contact number within 60 minutes following laboratory release of the critical test result(s). In the event that contact is not made within the 60-minute period, we continue to telephone until the designated party is reached and the result is conveyed in compliance and adherence to the CAP.
Semi-Urgent Results—Semi-Urgent Results are defined by Mayo Clinic as those infectious disease-related results that are needed promptly to avoid potentially serious health consequences for the patient (or in the case of contagious diseases, potentially serious health consequences to other persons exposed to the patient) if not acknowledged and/or treated by the physician. While not included on the Critical Values List, this information is deemed important to patient care in compliance and adherence to the CAP.

To complement Mayo Medical Laboratories’ normal reporting mechanisms (eg, fax, interface), Mayo Medical Laboratories’ staff will telephone results identified as significant microbiology findings to the ordering facility within 2 hours following laboratory release of the result(s). In the event that contact is not made within the 2-hour period, we will continue to telephone until the responsible party is reached and the result is conveyed. In addition, in most instances, you will see the comment SIGNIFICANT RESULT appear on the final report.

For information regarding the Mayo Clinic Critical Value List, contact Mayo Medical Laboratories at 800-533-1710 or 507-266-5700 or visit mayomedicallaboratories.com.

Disclosures of Results
Under federal regulations, we are only authorized to release results to ordering physicians or other health care providers responsible for the individual patient’s care. Third parties requesting results, including requests directly from the patient, are directed to the ordering facility.

Fee Changes
Fees are subject to change without notification and complete pricing per accession number is available once accession number is final. Specific client fees are available by calling Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 or by visiting mayomedicallaboratories.com.

Framework for Quality
“Framework for Quality” is the foundation for the development and implementation of the quality program for Mayo Medical Laboratories. Our framework builds upon the concepts of quality control and quality assurance providing an opportunity to deliver consistent, high-quality and cost-effective service to our clients. In addition, our quality program enhances our ability to meet and exceed the requirements of regulatory/accreditation agencies and provide quality service to our customers.

A core principle at Mayo Medical Laboratories is the continuous improvement of all processes and services that support the care of patients. Our continuous improvement process focuses on meeting the needs of you, our client, to help you serve your patients.

“Framework for Quality” is composed of 12 “Quality System Essentials.” The policies, processes, and procedures associated with the “Quality System Essentials” can be applied to all operations in the path of workflow (eg, pre-analytical, analytical, and post-analytical). Performance is measured through constant monitoring of activities in the path of workflow and comparing performance through benchmarking internal and external quality indicators and proficiency testing.

Data generated by quality indicators drives process improvement initiatives to seek resolutions to system-wide problems. Mayo Medical Laboratories utilizes “Failure Modes and Effects Analysis (FMEA),” “Plan Do Study Act (PDSA),” “LEAN,” “Root Cause Analysis,” and “Six Sigma” quality improvement tools to determine appropriate remedial, corrective, and preventive actions.

Quality Indicators—Mayo Medical Laboratories produces hundreds of Key Performance Indicators for our business and operational areas, and we review them regularly to ensure that we continue to maintain our high standards. A sampling of these metrics includes:

- Pre-analytic performance indicators
- Lost specimens*
To facilitate timely and quality specimen processing and to ensure the integrity of test results, Mayo Medical Laboratories has established a planned, systematic program. This program includes definitions for several critical components:

- **On-time delivery**
- **Special handling calls**
- **Specimen acceptability**
- **Specimen identification**
- **Incoming defects**

**Analytic performance indicators** include:
- **Proficiency testing**
- **Test reliability**
- **Turnaround (analytic) times**
- **Quantity-not-sufficient (QNS) specimens**

**Post-analytic performance indicators** encompass:
- **Revised reports**
- **Critical value reports**

**Operational performance indicators** consist of:
- **Incoming call resolution**
- **Incoming call abandon rate**
- **Call completion rate**
- **Call in-queue monitoring**
- **Customer complaints**
- **Customer satisfaction surveys**

The system provides a planned, systematic program for defining, implementing, monitoring, and evaluating our services.

*Measured using Six Sigma defects per million (dpm) method.

**HIPAA Compliance**
Mayo Medical Laboratories is fully committed to compliance with all privacy, security, and electronic transaction code requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All services provided by Mayo Medical Laboratories that involve joint efforts will be done in a manner which enables our clients to be HIPAA and the College of American Pathologists (CAP) compliant.

**Infectious Material**
The Centers for Disease Control (CDC) in its regulations of July 21, 1980, has listed organisms/diseases for which special packaging and labeling must be applied. Required special containers and packaging instructions can be obtained from us by using the “Request for Supplies” form or by ordering from the online Supply Catalog at mayomedicallaboratories.com/customer-service/supplies/index.php.

Shipping regulations require that infectious substances affecting humans be shipped in a special manner. See “Infectious Material.” A copy of the regulations can be requested from the International Air Transport Association (IATA); they may be contacted by phone at 514-390-6770 or faxed at 514-874-2660.

**Informed Consent Certification**
Submission of an order for any tests contained in this catalog constitutes certification to Mayo Medical Laboratories by ordering physician that: (1) ordering physician has obtained “Informed Consent” of subject patient as required by any applicable state or federal laws with respect to each test ordered; and (2) ordering physician has obtained from subject patient authorization permitting Mayo Medical Laboratories to report results of each test ordered directly to ordering physician.

On occasion, we forward a specimen to an outside reference laboratory. The laws of the state where the reference laboratory is located may require written informed consent for certain tests. Mayo Medical Laboratories will request that ordering physician pursue and provide such consent. Test results may be delayed or denied if consent is not provided.
Non-Biologic Specimens
Due to the inherent exposure risk of non-biologic specimens, their containers, and the implied relationship to criminal, forensic, and medico-legal cases, Mayo Medical Laboratories does not accept nor refer non-biologic specimen types. Example specimens include: unknown solids and liquids in the forms of pills, powder, intravenous fluids, or syringe contents.

Patient Safety Goals
One of The Joint Commission National Patient Safety goals for the Laboratory Services Program is to improve the accuracy of patient identification by using at least 2 patient identifiers when providing care, treatment, or services.

Mayo Medical Laboratories uses multiple patient identifiers to verify the correct patient is matched with the correct specimen and the correct order for the testing services. As a specimen is received at Mayo Medical Laboratories, the client number, patient name, and patient age date of birth are verified by comparing the labels on the specimen tube or container with the electronic order and any paperwork (batch sheet or form) which may accompany the specimen to be tested. When discrepancies are identified, the Mayo Laboratory call center will call the client to verify discrepant information to assure Mayo Medical Laboratories is performing the correct testing for the correct patient. When insufficient or inconsistent identification is submitted, Mayo Medical Laboratories will recommend that a new specimen be obtained, if feasible.

In addition, Anatomic Pathology consultation services require the Client Pathology Report. The pathology report is used to match the patient name, patient age and/or date of birth, and pathology case number. Since tissue blocks and slides have insufficient space to print the patient name on the block, the pathology report provides Mayo Medical Laboratories another mechanism to confirm the patient identification with the client order and labels on tissue blocks and slides.

Parallel Testing
Parallel testing may be appropriate in some cases to re-establish patient baseline results when converting to a new methodology at Mayo Medical Laboratories. Contact your Regional Manager at 800-533-1710 or 507-266-5700 for further information.

Proficiency Testing
We are a College of American Pathologists (CAP)-accredited, CLIA-licensed facility that voluntarily participates in many diverse external and internal proficiency testing programs. It is Mayo Medical Laboratories’ expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing (42 CFR 493.801), including a prohibition on discussion about samples or results and sharing of proficiency testing materials with Mayo Medical Laboratories during the active survey period. Referring of specimens is acceptable for comparison purposes when outside of the active survey period or when an approved proficiency testing program is not available for a given analyte.

Mayo Medical Laboratories’ proficiency testing includes participation in programs conducted by CAP and the Centers for Disease Control and Prevention (CDC) along with independent state, national, and international programs. Our participation includes:

- American Association of Bioanalysts (AAB)
- AABB (Formerly American Association of Blood Banks) Immunohematology Reference Laboratory
- The Binding Site
- Centers for Disease Control and Lipid Standardization Program
- Centers for Disease Control and Prevention (CDC)
- College of American Pathologists (CAP) Surveys
- Cystic Fibrosis European Network
- EMQN EQA Scheme
• Health Canada Interlaboratory Comparison Program
• International Tay-Sachs Program
• Laboratoire De Biochimie Et De Toxicologie (Interlaboratory Aluminum Quality Control)
• Le Centre de Toxicologie du Quebec – Quality Assessment Scheme
• Le Centre de Toxicologie du Quebec – Comparison Program
• New York State Department of Health
• Pennsylvania State Department of Health
• Vitamin D External Quality Assessment Scheme
• Wisconsin State Laboratory of Hygiene
• Women & Infants Hospital (WIH) First Trimester

We conduct internal assessments and comparability studies to ensure the accuracy and reliability of patient testing when an approved proficiency-testing program is not available or additional quality monitoring is desired. We comply with the regulations set forth in Clinical Laboratory Improvement Amendments (CLIA-88), the Occupational Safety and Health Administration (OSHA), or the Centers for Medicare & Medicaid Services (CMS).

It is Mayo Medical Laboratories’ expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing including a prohibition on discussion about samples or results and sharing of proficiency testing materials with Mayo Medical Laboratories during the active survey period. Referring of specimens is acceptable for comparison purposes when outside of the active survey period or when an approved proficiency-testing program is not available for a given analyte.

Radioactive Specimens
Specimens from patients receiving radioactive tracers or material should be labeled as such. All incoming shipment arriving at Mayo Medical Laboratories are routed through a detection process in receiving to determine if the samples have any levels of radioactivity. If radioactive levels are detected, the samples are handled via an internal process that assures we do not impact patient care and the safety of our respective staff. This radioactivity may invalidate the results of radioimmunoassays (RIA).

Record Retention
Mayo Medical Laboratories retains all test requisitions and patient test results at a minimum for the retention period required to comply with and adhere to the CAP. A copy of the original report can be reconstructed including reference ranges, interpretive comments, flags, and footnotes with the source system as the Department of Laboratory Medicine’s laboratory information system.

Referral of Tests to Another Laboratory
Mayo Medical Laboratories forwards tests to other laboratories as a service to its clients. This service should in no way represent an endorsement of such test or referral laboratory or warrant any specific performance for such test. Mayo Medical Laboratories will invoice for all testing referred to another laboratory at the price charged to Mayo Medical Laboratories. In addition, Mayo Medical Laboratories will charge an administrative fee per test for such referral services.

Reflex Testing
Mayo Medical Laboratories identifies tests that reflex when medically appropriate. In many cases, Mayo Medical Laboratories offers components of reflex tests individually as well as together. Clients should familiarize themselves with the test offerings and make a decision whether to order a reflex test or an individual component. Clients, who order a reflex test, can request to receive an “Additional Testing Notification Report” which indicates the additional testing that has been performed. This report will be faxed to the client. Clients who wish to receive the “Additional Testing Notification Report” should contact their Regional Manager or Regional Service Representative.
Reportable Disease
Mayo Medical Laboratories, in compliance with and adherence to the College of American Pathologists (CAP) Laboratory General Checklist (CAP GEN. 20373) strives to comply with laboratory reporting requirements for each state health department regarding reportable disease conditions. We report by mail, fax, and/or electronically, depending upon the specific state health department regulations. Clients shall be responsible for compliance with any state specific statutes concerning reportable conditions, including, but not limited to, birth defects registries or chromosomal abnormality registries. This may also include providing patient address/demographic information. Mayo Medical Laboratories’ reporting does not replace the client/physician responsibility to report as per specific state statutes.

Request for Physician Name and Number
Mayo Medical Laboratories endeavors to provide high quality, timely results so patients are able to receive appropriate care as quickly as possible. While providing esoteric reference testing, there are times when we need to contact the ordering physician directly. The following are 2 examples:

When necessary to the performance of a test, the ordering physician’s name and phone number are requested as part of “Specimen Required.” This information is needed to allow our physicians to make timely consultations or seek clarification of requested services. If this information is not provided at the time of specimen receipt, we will call you to obtain the information. By providing this information up front, delays in patient care are avoided.

In some situations, additional information from ordering physician is necessary to clarify or interpret a test result. At that time, Mayo Medical Laboratories will request physician’s name and phone number so that 1 of our staff can consult with the physician.

We appreciate your rapid assistance in supplying us with the ordering physician’s name and phone number when we are required to call. Working together, we can provide your patients with the highest quality testing services in the shortest possible time.

Special Handling
Mayo Medical Laboratories serves as a reference laboratory for clients around the country and world. Our test information, including days and time assays are performed as well as analytic turnaround time, is included under each test listing in the Test Catalog on mayomedicallaboratories.com. Unique circumstances may arise with a patient resulting in a physician request that the specimen or results receive special handling. There are several options available. These options can only be initiated by contacting Mayo Laboratory Inquiry at 800-533-1710 and providing patient demographic information.

There is a nominal charge associated with any special handling.

- **Hold:** If you would like to send us a specimen and hold that specimen for testing pending initial test results performed at your facility, please call Mayo Laboratory Inquiry. We will initiate a hold and stabilize the specimen until we hear from you.
- **Expedite:** If you would like us to expedite the specimen to the performing laboratory, you can call Mayo Laboratory Inquiry and request that your specimen be expedited. Once the shipment is received in our receiving area, we will deliver the specimen to the performing laboratory for the next scheduled analytic run. We will not set up a special run to accommodate an expedite request.
- **STAT:** In rare circumstances, STAT testing from the reference laboratory may be required for patients who need immediate treatment. These cases typically necessitate a special analytic run to turn results around as quickly as possible. To arrange STAT testing, please have your pathologist, physician, or laboratory director call Mayo Laboratory Inquiry. He/she will be connected with one of our medical directors to consult about the patient’s case. Once mutually agreed upon that there is a need for a STAT, arrangements will be made to assign resources to run the testing on a STAT basis when the specimen is received.
Specimen Identification Policy
In compliance with and adherence to the CAP and the Joint Commission’s 2008 Patient Safety Goals (1A), Mayo Medical Laboratories’ policy states that all specimens received for testing must be correctly and adequately labeled to assure positive identification. Specimens must have 2 person-specific identifiers on the patient label. Person-specific identifiers may include: accession number, patient’s first and last name, unique identifying number (e.g., medical record number), or date of birth. Specimens are considered mislabeled when there is a mismatch between the person-specific identifiers on the specimen and information accompanying the specimen (e.g., computer system, requisition form, additional paperwork).

When insufficient or inconsistent identification is submitted, Mayo Medical Laboratories will recommend that a new specimen be obtained, if feasible.

Specimen Rejection
All tests are unique in their testing requirements. To avoid specimen rejection or delayed turnaround times, please check the “Specimen Required” field within each test. You will be notified of rejected or problem specimens upon receipt.

Please review the following conditions prior to submitting a specimen to Mayo Medical Laboratories:
- Full 24 hours for timed urine collection
- pH of urine
- Lack of hemolysis/lipemia
- Specimen type (plasma, serum, whole blood, etc.)
- Specimen volume
- Patient information requested
- Proper identification of patient/specimen
- Specimen container (metal-free, separation gel, appropriate preservative, etc.)
- Transport medium
- Temperature (ambient, frozen, refrigerated)

Specimen Volume
The “Specimen Required” section of each test includes 2 volumes - preferred volume and minimum volume. Preferred volume has been established to optimize testing and allows the laboratory to quickly process specimen containers, present containers to instruments, perform test, and repeat test, if necessary. Many of our testing processes are fully automated; and as a result, this volume allows hands-free testing and our quickest turnaround time (TAT). Since patient values are frequently abnormal, repeat testing, dilutions, or other specimen manipulations often are required to obtain a reliable, reportable result. Our preferred specimen requirements allow expeditious testing and reporting.

When venipuncture is technically difficult or the patient is at risk of complications from blood loss (e.g., pediatric or intensive care patients), smaller volumes may be necessary. Specimen minimum volume is the amount required to perform an assay once, including instrument and container dead space.

When patient conditions do not mandate reduced collection volumes, we ask that our clients submit preferred volume to facilitate rapid, cost-effective, reliable test results. Submitting less than preferred volume may negatively impact quality of care by slowing TAT, increasing the hands-on personnel time (and therefore cost) required to perform test.

Mayo Clinic makes every possible effort to successfully test your patient’s specimen. If you have concerns about submitting a specimen for testing, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700. Our staff will discuss the test and specimen you have available. While in some cases specimens are inadequate for desired test, in other cases, testing can be performed using alternative techniques.
Supplies
Shipping boxes, specimen vials, special specimen collection containers, and request forms are supplied without charge. Supplies can be requested using 1 of the following methods: use the online ordering functionality available at mayomedicallaboratories.com/supplies or call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

Test Classifications
Analytical tests offered by Mayo Medical Laboratories are classified according to the FDA labeling of the test kit or reagents and their usage. Where appropriate, analytical test listings contain a statement regarding these classifications, test development, and performance characteristics. The classifications include:

- **Standard Method** - This test uses a standard method. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements.
- **FDA Approved, Cleared, or Exempt (IVD)** - This test has been cleared or approved by the U.S. Food and Drug Administration (or is exempt from FDA review) and is used per manufacturer’s instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.
- **FDA Modified** - This test has been modified from the manufacturer's instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements.
- **Analyte Specific Reagent (ASR)** - This test was developed using an analyte specific reagent. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.
- **Laboratory Developed Test** - This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.
- **Investigational Use Only (IUO)** - This test uses a kit labeled by the manufacturer as "investigational use only" and it is used per manufacturer's instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.
- **Research Use Only (RUO)** - This test uses a reagent or kit labeled by the manufacturer as "research use only" and it is used per manufacturer's instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

Test Development Process
Mayo Medical Laboratories serves patients and health care providers from Mayo Clinic, Mayo Health System, and our reference laboratory clients worldwide. We are dedicated to providing clinically useful, cost-effective testing strategies for patient care. Development, validation, and implementation of new and improved laboratory methods are major components of that commitment.

Each assay utilized at Mayo Clinic, whether developed on site or by others, undergoes an extensive validation and performance documentation period before the test becomes available for clinical use. Validations follow a standard protocol that includes:

- Accuracy
- Precision
- Sensitivity
- Specificity and interferences
- Reportable range
- Linearity
- Specimen stability
- Specimen type comparisons
- Urine preservative studies: stability at ambient, refrigerated, and frozen temperatures and with 7 preservatives; at 1, 3, and 7 days
- Comparative evaluation: with current and potential methods
- Reference values: using medically evaluated healthy volunteers, male and female, across age groups. The number of observations required for each test is determined by biostatistic analysis. Unless otherwise stated, reference values provided by Mayo Medical Laboratories are derived from studies performed in our laboratories. When reference values are obtained from other sources, the source is indicated in the “Reference Values” field.
- Workload recording
- Limitations of the assay
- Clinical utility and interpretation: written by Mayo Clinic medical experts, electronically available (MayoAccess™)

Test Result Call-Backs
Results will be phoned to a client when requested from the client (either on Mayo Medical Laboratories’ request form or from a phone call to Mayo Medical Laboratories from the client).

Time-Sensitive Specimens
Please contact Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 prior to sending a specimen for testing of a time-sensitive nature. Relay the following information: facility name, account number, patient name and/or Mayo Medical Laboratories’ accession number, shipping information (ie, courier service, FedEx®, etc.), date to be sent, and test to be performed. Place specimen in a separate Mayo Medical Laboratories’ temperature appropriate bag. Please write “Expedite” in large print on outside of bag.

Turnaround Time (TAT)
Mayo Medical Laboratories’ extensive test menu reflects the needs of our own health care practice. We are committed to providing the most expedient TAT possible to improve diagnosis and treatment. We consider laboratory services as part of the patient care continuum wherein the needs of the patient are paramount. In that context, we strive to fulfill our service obligations. Our history of service and our quality metrics will document our ability to deliver on all areas of service including TAT.

Mayo Medical Laboratories defines TAT as the analytical test time (the time from which a specimen is received at the testing location to time of result) required. TAT is monitored continuously by each performing laboratory site within the Mayo Clinic Department of Laboratory Medicine and Pathology. For the most up-to-date information on TAT for individual tests, please visit us at mayomedicallaboratories.com or contact our Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

Unlisted Tests
Mayo Medical Laboratories does not list all available test offerings in the paper catalog. New procedures are developed throughout the year; therefore, some tests are not listed in this catalog. Although we do not usually accept referred tests of a more routine type, special arrangements may be made to provide your laboratory with temporary support during times of special need such as sustained instrumentation failure. For information about unlisted tests, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.
Pompe Disease, Full Gene Analysis

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive condition caused by deficiency of acid alpha-glucosidase. Enzyme insufficiency results in symptoms such as muscle weakness, cardiomyopathy, and respiratory problems. Mutations in the GAA gene (which encodes acid alpha-glucosidase) are associated with Pompe disease. The diagnosis of this heterogeneous condition relies on both clinical and laboratory evaluation. Clinically, the condition is categorized into infantile and late-onset forms based on age of onset, organ involvement, and rate of progression. The infantile form (or classic Pompe disease) is the most severe form and is characterized by early onset and rapid progression of cardiac, liver, and muscle problems resulting in death within the first year. The infantile variant form has a similar age of onset but a milder clinical presentation. On the less severe end of the spectrum is the late-onset form with childhood, juvenile, or adult onset. The rate of progression and severity of symptoms is quite variable, particularly in the late-onset forms. The incidence varies by clinical type and ethnic population; the combined incidence is approximately 1 in 40,000 individuals. Biochemical testing of acid alpha-glucosidase in blood spot specimens or fibroblasts is useful for individuals with a suspected diagnosis of Pompe disease (GAABS / Acid Alpha-Glucosidase, Blood Spot). When clinical manifestations and results of that analysis are supportive of a diagnosis of Pompe disease, mutation analysis of the GAA gene is warranted. Over 250 different mutations have been identified in this gene including point mutations and large deletions. GAA full gene sequencing provided by this test will detect 2 mutations in approximately 83% to 93% of individuals with confirmed GAA enzyme deficiency. Identification of mutations provides confirmation of the diagnosis and allows for subsequent testing of at risk family members.

Useful For: Confirmation of diagnosis of Pompe disease (as a follow-up to biochemical analyses)

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


1,25-Dihydroxyvitamin D, Serum

Clinical Information: Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols including ergocalciferol D2 from plants and cholecalciferol D3 from animals. Vitamin D in the body is derived from 2 sources: exogenous (dietary: D2 and D3) and endogenous (biosynthesis: D3). Endogenous D3 is produced in the skin from 7-dehydrocholesterol, under the influence of ultraviolet light. Both forms of vitamin D are of similar biologic activity. Vitamin D is rapidly metabolized in the liver to form 25-hydroxy (OH) vitamin D. Additional hydroxylation of 25-OH vitamin D takes place in the kidney by 1-alpha hydroxylase, under the control of parathyroid hormone, to yield 1,25-dihydroxy vitamin D. 1,25-Dihydroxy vitamin D is the most potent vitamin D metabolite. It stimulates calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and parathyroid hormone. 1,25-Dihydroxy vitamin D levels may be high in primary hyperparathyroidism and in physiologic hyperparathyroidism secondary to low calcium or vitamin D intake. Some patients with granulomatous diseases (eg, sarcoidosis) and malignancies containing...
nonregulated 1-alpha hydroxylase in the lesion may have elevated 1,25-dihydroxy vitamin D levels and hypercalcemia. 1,25-Dihydroxy vitamin D levels are decreased in hypoparathyroidism and in chronic renal failure. While 1,25-dihydroxy vitamin D is the most potent vitamin D metabolite, levels of the 25-OH forms of vitamin D more accurately reflect the body's vitamin D stores. Consequently, 25HDN / 25-Hydroxyvitamin D2 and D3, Serum is the preferred initial test for assessing vitamin D status. However, in the presence of renal disease, 1,25-dihydroxy vitamin D levels may be needed to adequately assess vitamin D status.

**Useful For:** As a second-order test in the assessment of vitamin D status, especially in patients with renal disease Investigation of some patients with clinical evidence of vitamin D deficiency (eg, vitamin D-dependent rickets due to hereditary deficiency of renal 1-alpha hydroxylase or end-organ resistance to 1,25-dihydroxy vitamin D) Differential diagnosis of hypercalcemia

**Interpretation:** 1,25-Dihydroxy vitamin D concentrations are low in chronic renal failure and hypoparathyroidism. 1,25-Dihydroxy vitamin D concentrations are high in sarcoidosis and other granulomatous diseases, some malignancies, primary hyperparathyroidism, and physiologic hyperparathyroidism. 1,25-dihydroxy vitamin D concentrations are not a reliable indicator of vitamin D toxicity; normal (or even low) results may be seen in such cases.

**Reference Values:**

Males
- <16 years: 24-86 pg/mL
- > or =16 years: 18-64 pg/mL

Females
- <16 years: 24-86 pg/mL
- > or =16 years: 18-78 pg/mL

**Clinical References:**

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**11-Dehydro-Thromboxane B2, Urine**

**Clinical Information:** Antiplatelet medications are frequently utilized in the prevention of stroke, myocardial infarction, and vascular thrombotic diseases due to the fundamental role of platelet aggregation in a variety of atherothrombotic processes. Modulation of the prostaglandin thromboxane A2 (TxA2) pathway is 1 of the pivotal routes of activation involved in stimulating platelet aggregation. Synthesis of TxA2 is mediated in platelets by the cyclooxygenase 1 (COX-1) enzyme, which must be functional for stimulating the production of TxA2 from arachidonic acid. The importance of TxA2 is demonstrated by the reduction in risk of myocardial infarction (MI) or death in patients with acute coronary syndrome (ACS) following administration of aspirin, which irreversibly inhibits platelet COX-1 and inhibits the production of TxA2. TxA2 has an extremely short half-life, converting to 2 stable, inactive metabolites: 11-dehydro-thromboxane B2 (TxB2) and 2, 3-dinor-11-dehydrothromboxane B2. Excretion of TxB2 in the urine has been shown to reflect in vivo platelet activation. Elevated concentrations of TxB2 have been noted in up to 85% of patients with acute ischemic stroke and demonstrate further diagnostic and prognostic utility in patients with ACS. Aspirin therapy has been reported to reduce cardiovascular events in men and women by up to 40%. However, use of aspirin is not without risk and is associated with higher frequencies of gastrointestinal bleeding and hemorrhagic stroke. Identification of patients most likely to benefit from antiplatelet therapy with aspirin or other pharmaceutical agents has great clinical utility. Quantitation of urinary TxB2 offers an advantage over platelet-activation markers measured in plasma or blood because measurements are not subject to interference from in vitro platelet activation, which commonly occurs as a result of preanalytical variables such as local vein trauma or insufficient anticoagulation during phlebotomy. Measurement of urine TxB2 may be performed in patients to assess the effectiveness of specific inhibition in the TxA2 pathway, along with identification of a patientâ€™s ability to benefit from antiplatelet therapy, and their associated risk.

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for developing future cardiovascular events.

**Useful For:** Assessing if a patient will derive benefit from aspirin therapy. Determining an individual’s risk of coronary heart disease and stroke. Identifying the effectiveness of antiplatelet therapies.

**Interpretation:** The normal reference range was derived from an in-house normal donor study with individuals who were self-reported as not taking any aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or other lipid-lowering therapies. Elevated concentrations of urine thromboxane B2 (TxB2) may indicate an increase in platelet activation and thrombosis resulting from atherosclerotic deposits or other vascular obstructions and may identify those individuals who may be at increased risk for an ischemic cardiovascular event. Elevations of TxB2 in patients already receiving antiplatelet therapies suggest a failure in the suppression of laboratory-assessed platelet function, a continued hypercoagulable state, and alternative antithrombotic or antiplatelet therapies may be considered. The liquid chromatography-tandem mass spectrometry method is specific for TxB2 and is not subject to interference from the other metabolite of thromboxane A2, the 2,3-dinor-TxB2 component.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; or =18 years</td>
<td>0-2,211 pg/mg creatinine</td>
<td>Reference values have not been established for patients who are &lt;18 years of age. Reference intervals apply to patients not taking agents known to influence platelet function (aspirin or other nonsteroidal anti-inflammatory drugs, thienopyridines, etc). Healthy individuals taking aspirin typically have 11-dehydro-thromboxane B2 concentrations below 500 pg/mg creatinine using this method.</td>
</tr>
</tbody>
</table>

**Clinical References:**

**11-Deoxycortisol Quantitative by HPLC-MS/MS, Serum**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 â€“ 28 weeks)</td>
<td>110 â€“ 1376 ng/dL</td>
<td>110 â€“ 1376 ng/dL</td>
</tr>
<tr>
<td>Premature (29 â€“ 36 weeks)</td>
<td>70 â€“ 455 ng/dL</td>
<td>70 â€“ 455 ng/dL</td>
</tr>
<tr>
<td>Full Term (1 â€“ 5 months)</td>
<td>10 â€“ 200 ng/dL</td>
<td>10 â€“ 200 ng/dL</td>
</tr>
<tr>
<td>6 â€“ 11 months</td>
<td>10 â€“ 276 ng/dL</td>
<td>10 â€“ 276 ng/dL</td>
</tr>
<tr>
<td>1 â€“ 3 years</td>
<td>7 â€“ 247 ng/dL</td>
<td>7 â€“ 202 ng/dL</td>
</tr>
<tr>
<td>4 â€“ 6 years</td>
<td>8 â€“ 291 ng/dL</td>
<td>8 â€“ 235 ng/dL</td>
</tr>
<tr>
<td>7 â€“ 9 years</td>
<td>Less than or equal to 94 ng/dL</td>
<td>Less than or equal to 120 ng/dL</td>
</tr>
<tr>
<td>10 â€“ 12 years</td>
<td>Less than or equal to 123 ng/dL</td>
<td>Less than or equal to 92 ng/dL</td>
</tr>
<tr>
<td>13 â€“ 15 years</td>
<td>Less than or equal to 107 ng/dL</td>
<td>Less than or equal to 95 ng/dL</td>
</tr>
<tr>
<td>16 â€“ 17 years</td>
<td>Less than or equal to 47 ng/dL</td>
<td>Less than or equal to 106 ng/dL</td>
</tr>
<tr>
<td>18 years and older</td>
<td>Less than 33 ng/dL</td>
<td>Less than 50 ng/dL</td>
</tr>
</tbody>
</table>
11-Deoxycortisol, Serum

Clinical Information: 11-Deoxycortisol (Compound S) is the immediate precursor of cortisol: 11 beta-hydroxylase 11-deoxycortisol -> cortisol and is typically increased when adrenocorticotropic hormone (ACTH) levels are increased (eg, Cushing disease, ACTH-producing tumors) or in 11 beta-hydroxylase deficiency, a rare subform of congenital adrenal hyperplasia (CAH). In CAH due to 11 beta-hydroxylase deficiency, cortisol levels are low, resulting in increased pituitary ACTH production and increased serum and urine 11-deoxycortisol levels. Pharmacological blockade of 11 beta-hydroxylase with metyrapone can be used to assess the function of the hypothalamic-pituitary-adrenal axis (HPA). In this procedure metyrapone is administered to patients, and serum 11-deoxycortisol levels or urinary 17-hydroxy steroid levels are measured either at baseline (midnight) and 8 hours later (overnight test), or at baseline and once per day during a 2-day metyrapone test (4-times a day metyrapone administration over 2 days). Two-day metyrapone testing has been largely abandoned because of the logistical problems of multiple timed urine and blood collections and the fact that overnight testing provides very similar results. In either case, the normal response to metyrapone administration is a fall in serum cortisol levels, triggering a rise in pituitary ACTH secretion, which, in turn, leads to a rise in 11-deoxycortisol levels due to the ongoing 11-deoxycortisol-to-cortisol conversion block. In the diagnostic workup of suspected adrenal insufficiency, the results of overnight metyrapone testing correlate closely with the gold standard of HPA-axis assessment, insulin hypoglycemia testing. Combining 11-deoxycortisol measurements with ACTH measurements during metyrapone testing further enhances the performance of the test. Impairment of any component of the HPA-axis results in a subnormal rise in 11-deoxycortisol levels. By contrast, standard-dose or low-dose ACTH(1-24) (cosyntropin)-stimulation testing, which forms the backbone for diagnosis of primary adrenal failure (Addison disease), only assess the ability of the adrenal cells to respond to ACTH stimulation. While this allows unequivocal diagnosis of primary adrenal failure, in the setting of secondary or tertiary adrenal insufficiency, metyrapone testing is more sensitive and specific than either standard-dose or low-dose ACTH(1-24)-stimulation testing. Metyrapone testing is also sometimes employed in the differential diagnosis of Cushing syndrome. In Cushing disease (pituitary-dependent ACTH overproduction), the ACTH-hypersecreting pituitary tissue remains responsive to the usual feedback stimuli, just at a higher "set-point" than in the normal state, resulting in increased ACTH secretion and 11-deoxycortisol production after metyrapone administration. By contrast, in Cushing syndrome due to primary adrenal corticosteroid oversecretion or ectopic ACTH secretion, pituitary ACTH production is appropriately shut down and there is usually no further rise in ACTH and, hence 11-deoxycortisol, after metyrapone administration. The metyrapone test has similar sensitivity and specificity to the high-dose dexamethasone suppression test in the differential diagnosis of Cushing disease, but is less widely used because of the lack of availability of an easy, automated 11-deoxycortisol assay. In recent years, both tests have been supplanted to some degree by corticotropin-releasing hormone (CRH)-stimulation testing with petrosal sinus serum ACTH sampling. See Steroid Pathways in Special Instructions.

Useful For: Diagnostic workup of patients with congenital adrenal hyperplasia Part of metyrapone testing in the workup of suspected secondary or tertiary adrenal insufficiency Part of metyrapone testing in the differential diagnostic workup of Cushing syndrome

Interpretation: In a patient suspected of having congenital adrenal hyperplasia (CAH), elevated serum 11-deoxycortisol levels indicate possible 11 beta-hydroxylase deficiency. However, not all patients will show baseline elevations in serum 11-deoxycortisol levels. In a significant proportion of cases, increases in 11-deoxycortisol levels are only apparent after adrenocorticotropic hormone (ACTH)(1-24) stimulation.

<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Less than or equal to</th>
<th>Less than or equal to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>94 ng/dL</td>
<td>105 ng/dL</td>
</tr>
<tr>
<td>Stage II</td>
<td>136 ng/dL</td>
<td>108 ng/dL</td>
</tr>
<tr>
<td>Stage III</td>
<td>99 ng/dL</td>
<td>111 ng/dL</td>
</tr>
<tr>
<td>Stage IV &amp; V</td>
<td>50 ng/dL</td>
<td>83 ng/dL</td>
</tr>
<tr>
<td>After metyrapone stimulation</td>
<td>Greater than 8000 ng/dL</td>
<td>Greater than 8000 ng/dL</td>
</tr>
</tbody>
</table>
indicative of probable adrenal insufficiency. The test cannot reliably distinguish between primary and secondary or tertiary causes of adrenal failure, as neither patients with pituitary failure, nor those with primary adrenocortical failure, tend to show an increase of 11-deoxycortisol levels after metyrapone is administered. See Steroid Pathways in Special Instructions.

Reference Values:
< or ≥18 years: <344 ng/dL
>18 years: 10-79 ng/dL


FD Sox
11-Desoxycortisol (Specific Compound S)
Reference Values:
<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>110-1376</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>48-579</td>
</tr>
<tr>
<td>Newborn Day 3</td>
<td>13-147</td>
</tr>
<tr>
<td>31d-11m</td>
<td>&lt;10-156</td>
</tr>
<tr>
<td>Prepubertal 8:00 AM</td>
<td>20-155</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>12-158</td>
</tr>
</tbody>
</table>

THCMX
11-nor-Delta-9-Tetrahydrocannabinol-9-Carboxylic Acid (Carboxy-THC) Confirmation, Chain of Custody, Meconium

Clinical Information: Marijuana and other psychoactive products obtained from the plant Cannabis sativa are the most widely used illicit drugs in the world. (1) Marijuana has unique behavioral effects that include feelings of euphoria and relaxation, altered time perception, impaired learning and memory, lack of concentration, and mood changes (eg, panic reactions and paranoia). Cannabis sativa produces numerous compounds collectively known as cannabinoids including delta-9-tetrahydrocannabinol (THC), which is the most prevalent and produces most of the characteristic pharmacological effects of smoked marijuana. (2) THC undergoes rapid hydroxylation by the cytochrome (CYP) enzyme system to form the active metabolite 11-hydroxy-THC. Subsequent oxidation of 11-hydroxy-THC produces the inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH; carboxy-THC). THC-COOH and its glucuronide conjugate have been identified as the major end-products of metabolism. THC is highly lipid soluble, resulting in its concentration and prolonged retention in fat tissue. (3) Cannabinoids cross the placenta, but a dose-response relationship or correlation has not been established between the amount of marijuana use in pregnancy and the levels of cannabinoids found in meconium, the first fecal matter passed by the neonate. (4, 5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing amniotic fluid. (5) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. (6) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. (5) Chain of custody is a record of
the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid > or =10 ng/g is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations

**Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by LC-MS/MS: 10 ng/g**

**Clinical References:**


**Clinical Information:**

Marijuana and other psychoactive products obtained from the plant Cannabis sativa are the most widely used illicit drugs in the world.(1) Marijuana has unique behavioral effects that include feelings of euphoria and relaxation, altered time perception, impaired learning and memory, lack of concentration, and mood changes (eg, panic reactions and paranoia). Cannabis sativa produces numerous compounds collectively known as cannabinoids including delta-9-tetrahydrocannabinol (THC), which is the most prevalent and produces most of the characteristic pharmacological effects of smoked marijuana.(2) THC undergoes rapid hydroxylation by the cytochrome (CYP) enzyme system to form the active metabolite 11-hydroxy-THC. Subsequent oxidation of 11-hydroxy-THC produces the inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH; carboxy-THC). THC-COOH and its glucuronide conjugate have been identified as the major end-products of metabolism. THC is highly lipid soluble, resulting in its concentration and prolonged retention in fat tissue.(3) Cannabinoids cross the placenta, but a dose-response relationship or correlation has not been established between the amount of marijuana use in pregnancy and the levels of cannabinoids found in meconium, the first fecal matter passed by the neonate.(4,5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing amniotic fluid.(5) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(6) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(5)
Useful For: Detection of in utero drug exposure up to 5 months before birth

Interpretation: The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid > or =10 ng/g is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by LC-MS/MS: 10 ng/g


14-3-3 Protein, Spinal Fluid

Clinical Information: The 14-3-3 proteins are a group of highly conserved proteins composed of several isoforms that are involved in the regulation of protein phosphorylation and mitogen-activated protein kinase pathways. They exist in vivo as dimers of the various isoforms with apparent molecular mass of 30 kDa on sodium dodecyl sulfate polyacrylamide gel electrophoresis and 60 kDa on gel chromatography. Sequence homology among the various isoforms ranges from 22% to100%. The beta, gamma, and theta isoforms are found in tissues of the nervous system. Detectable 14-3-3 protein in the cerebrospinal fluid (CSF) is indicative of substantial, relatively rapid neuronal destruction. Increased CSF concentrations of 14-3-3 proteins have been described in patients with various forms of Creutzfeldt-Jakob disease (CJD), some other rapidly progressive dementias, and a large range of other vascular, inflammatory, neoplastic, and metabolic central nervous system (CNS) disorders (see Cautions), which can be associated with significant and rapid neuronal destruction. The main clinical use of 14-3-3 measurements is in the differential diagnosis of dementia, in particular to distinguish CJD and its variants from other dementias. The most common forms of dementia (progressive multi-infarct dementia and Alzheimer disease) are uncommonly associated with elevated CSF levels of 14-3-3, presumably because of their slow pace of progression. CJD is an incurable neurodegenerative disease caused by accumulation of self-catalytically malfolded endogenous prion proteins in the CNS. Its cause is most commonly sporadic, but it can be inherited (mutations that predispose to malfolding) or acquired (iatrogenic transmission by infected human tissues or tissue extracts or surgical procedures, or by ingestion of some animal products that contain malfolded prion proteins). The diagnosis of CJD is highly complex and involves clinical history and neurologic examination, electroencephalographs (EEG), magnetic resonance imaging (MRI), and exclusion of other possible causes of dementia, in addition to CSF examination. Several, slightly different scoring systems are in use to integrate these parameters into a final diagnosis of possible, probable, or definite CJD. The most widely accepted of these scoring systems is the WHO set of diagnostic criteria for sporadic CJD from 1998 (see Interpretation).

Useful For: Supporting, in conjunction with other tests, a diagnosis of Creutzfeldt-Jakob disease in patients with rapidly progressive dementia when other neurodegenerative conditions have been excluded.

Interpretation: A concentration of 14-3-3 protein in cerebrospinal fluid (CSF) of > or =1.5 ng/mL supports the diagnosis of Creutzfeldt-Jakob disease (CJD) in patients who have been carefully preselected based on various diagnostic criteria. CSF 14-3-3 measurement is particularly helpful in sporadic CJD, where it is used as 1 of several diagnostic criteria. Sporadic CJD World Health Organization (WHO)
diagnostic criteria from 1998: 1. Definitive CJD: -Neuropathological diagnosis by standard techniques AND/OR immunohistochemistry AND/OR Western blot confirmed protease-resistant prion protein AND/OR presence of scrapie-associated fibrils. 2. Probable CJD: -Progressive dementia -At least 2 of the following symptoms: -Myoclonus, pyramidal/extrapyramidal, visual or cerebellar, akinetic mutism -Positive electroencephalographs (EEG) (periodic epileptiform discharges) AND/OR positive CSF 14-3-3 protein and <2 years disease duration -No alternate diagnosis. 3. Possible CJD: -Progressive dementia -At least 2 of the following symptoms: -Myoclonus, pyramidal/extrapyramidal, visual or cerebellar, akinetic mutism -No supportive EEG and <2 years disease duration. Recently proposed, but not yet universally accepted, amendments to these criteria center on including magnetic resonance imaging (MRI) high-signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) as diagnostic criteria for probable CJD. The USA Center of Disease Control and Prevention supports these modified WHO criteria as of 2010 (http://www.cdc.gov/ncidod/dvrd/cjd/diagnostic_criteria.html). There is no established role for 14-3-3 measurement in the diagnosis of acquired or inherited CJD.

Reference Values:
Normal: < or =2.0 ng/mL
Elevated: >2.0 ng/mL

Clinical References:

**BP1F**

**15q Deletion, Type I and Type II Characterization, Prader-Willi/Angelman Syndromes, FISH**

**Clinical Information:** Prader-Willi (PWS) and Angelman (AS) syndromes are 2 distinct syndromes that can result from either a paternal or maternal deletion of 15q11-q13, respectively. Other mechanisms of inheritance include maternal uniparental disomy (UPD) in PWS, paternal UPD in AS, or abnormal methylation and gene expression. Both type I and type II 15q11-q13 deletions have been described. Type I deletions are larger deletions, spanning breakpoint (BP)1 and distal BP3 breakpoints, while type II deletions are smaller (approximately 500kb), spanning BP2 and BP3. Depending on the deletion type, behavioral differences have been reported in both PWS and AS patients. Type I patients have more severe phenotypes including delayed development and autistic features. Distinguishing between type I and type II deletions is useful in counseling PWS or AS patients. Type I and II deletions may be detected by evaluating the RP11-289D12 region on chromosome 15 with specific DNA probes. A +dic(15) marker chromosome (an extra or supernumerary dicentric chromosome 15) is often familial and is usually consistent with a normal phenotype, but depending on its size, the marker can be associated with PWS or AS. Larger dic(15) are usually new mutations and are associated with mental retardation and mild dysmorphic features. See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions for additional information.

**Useful For:** Differentiating between type I and type II deletions in patients with a known deletion of 15q11.1-11.3, causative of Prader-Willi syndrome or Angelman Evaluation of dic(15) marker chromosomes

**Interpretation:** Any individual with a normal signal pattern (2 signals) in each metaphase is
considered negative for a deletion in the region tested by this probe (see Cautions). Any patient with a
FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the region
tested by this probe. This test should be performed as a reflex test when a SNRPN or D15S10 deletion has
been detected by FISH analysis or in patients with a dic(15) chromosome lacking the SNRPN or D15S10
loci.

Reference Values:
An interpretive report will be provided.

subjects with Prader-Willi syndrome and type I and type II deletion and maternal disomy. Pediatrics 2004
including deletion size, on Prader-Willi syndrome phenotype: study of 75 patients. Clin Genet 2005
between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that
have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet 2003
Oct;73(4):898-925

D15F 35253

15q11.2 Duplication, FISH

Clinical Information: Individuals with autism spectrum disorders, individuals with supernumerary
chromosomes suspicious for a chromosome 15 origin, individuals with duplications of 15q11-q13
detected by multiplex ligation-dependent probe amplification (MLPA) or other testing methodologies (to
distinguish between interstitial tandem duplication and supernumerary marker). Cytogenetic abnormalities
at the 15q11-q13 locus are reported in up to 4% of patients with autism spectrum disorders. Duplications
in this chromosome region can occur as an interstitial tandem repeat or as a supernumerary isodicentric
chromosome 15, leading to trisomy or tetrasomy of genes at the 15q11-q13 locus. The majority of
interstitial tandem repeats in this region are not detectable by conventional chromosome analysis but can
be identified by FISH. Supernumerary chromosomes can often be identified by conventional chromosome
analysis but their origin must be confirmed by FISH analysis. Molecular analysis by MLPA can also
detect duplications of chromosome 15q, but FISH analysis is necessary to distinguish between interstitial
tandem duplication and a supernumerary marker. The phenotype associated with these abnormalities
depends largely on the amount of duplicated material, as well as parent of origin. Small dicentric markers
with little 15q material duplicated are often familial and result in a normal phenotype. Larger dicentric 15
markers are usually new mutations and result in mild dysmorphic features, mental retardation, and
behavioral abnormalities consistent with autism. Interstitial tandem duplications are associated with
autistic spectrum disorders when maternally inherited, but paternally inherited duplications are less likely
to cause phenotypic effects.

Useful For: Evaluating patients with autistic spectrum disorders for 15q11.1-11.3 region Confirming
the origin of supernumerary marker chromosomes suspected of being derived from chromosome 15
Resolving the origin when duplication of 15q11.1-11.3 is identified via molecular multiplex
ligation-dependent probe amplification analysis

Interpretation: Specimens with a normal signal pattern in metaphase and interphase cells are
considered negative for this probe. Specimens with a FISH signal pattern indicating duplication of the
critical region (3 signals) will be reported as having a duplication of the region tested by this probe.

JA, Johnson J, Peterson Kraai TL, et al: Genetic and clinical characterization of patients with an
interstitial duplication 15q11-q13, emphasizing behavioral phenotype and response to treatment. Am J
(2006). Clinical Findings in 33 subjects with large supernumerary marker (15) chromosomes and 3
17-Hydroxy Progesterone, Urine

**Clinical Information:** 17-Hydroxy Progesterone is a steroid derived primarily from enzymatic metabolism of Progesterone and 17-Hydroxy Pregnenolone. It is converted enzymatically to Androstenedione and 11-Deoxycortisol. It is produced in both the gonads and adrenal glands. It is excreted into the urine in conjugated and unconjugated forms of 17-Hydroxy Progesterone and as Pregnanetriol. This assay measures the total of the conjugated and unconjugated forms. It is stimulated by ACTH and suppressed by Dexamethasone. Levels of urine 17-Hydroxy Progesterone are greatly increased in patients with Polycystic Ovarian Disease and Congenital Adrenal Hyperplasia and show exaggerated responses to ACTH in these cases. 17-Hydroxy Progesterone is the marker steroid for determining cases of 21a-Hydroxylase Deficient Congenital Adrenal Hyperplasia. Urine levels are frequently elevated in patients with idiopathic hirsutism.

**Reference Values:**

Pediatric Reference Ranges:
- Newborns and Infants: 3 days to 1 year: Up to 50 ng/24 hrs
- Children: 1 - 8 years: Up to 300 ng/24 hrs

Adult Reference Ranges:
- Male: Up to 2.0 ug/24 hrs.
- Female: Up to 4.5 ug/24 hrs.

17-OHP

17-Hydroxypregnenolone, Serum

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at the position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase: 3-beta-HSD). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone (DHEA) is also converted to androstenedione by 3-beta-HSD and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternatively, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** As an ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase (3-beta-HSD) deficiency Analysis for 17-hydroxypregnenolone is also useful as part of a battery of tests to evaluate females with hirsutism or infertility; both can result from adult-onset CAH.

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always
requires the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxyprogrenolone and pregnenolone and dehydroepiandrosterone (DHEA) levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**

**CHILDREN**

**Males**
- Premature (26-28 weeks): 1,219-9,799 ng/dL
- Premature (29-36 weeks): 346-8,911 ng/dL
- Full term (1-5 months): 229-3,104 ng/dL
- 6 months-364 days: 221-1,981 ng/dL
- 1-2 years: 35-712 ng/dL
- 3-6 years: <277 ng/dL
- 7-9 years: <188 ng/dL
- 10-12 years: <393 ng/dL
- 13-15 years: 35-465 ng/dL
- 16-17 years: 32-478 ng/dL

**Females**
- Premature (26-28 weeks): 1,219-9,799 ng/dL
- Premature (29-36 weeks): 346-8,911 ng/dL
- Full term (1-5 months): 229-3,104 ng/dL
- 6 months-364 days: 221-1,981 ng/dL
- 1-2 years: 35-712 ng/dL
- 3-6 years: <277 ng/dL
- 7-9 years: <188 ng/dL
- 10-12 years: <393 ng/dL
- 13-15 years: <213 ng/dL
- 16-17 years: <424 ng/dL

**TANNER STAGES**
- Stage I: <209 ng/dL
- Stage II: <356 ng/dL
- Stage III: <451 ng/dL
- Stage IV-V: 35-478 ng/dL

**ADULTS**
- Males
  - > or =18 years: 55-455 ng/dL
- Females
  - > or =18 years: 31-455 ng/dL


**Clinical References:** 1. Wudy SA, Hartmann M, Svoboda M: Determination of

17-Hydroxyprogesterone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. The resulting hormone imbalances with reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (OHPG) and androgens can lead to life-threatening, salt-wasting crisis in the newborn period and incorrect gender assignment of virtualized females. Adult-onset CAH may result in hirsutism or infertility in females. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 position to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequent increased pituitary release of ACTH increases production of OHPG. But, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-hydroxysteroid dehydrogenase type 2 (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone respectively. OHPG is bound to both corticosteroid binding globulin and albumin and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests are available to diagnose disorders or steroid metabolism than pregnanetriol measurement. Most (90%) cases of CAH are due to mutations in the steroid 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione (ANST / Androstenedione, Serum) with decreased cortisol (CINP / Cortisol, Serum, LC-MS/MS). By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (FDOC / Deoxycorticosterone [DOC], Serum), respectively, are necessary for diagnosis. CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of OHPG, androstenedione, and cortisol. See Steroid Pathways in Special Instructions.

Useful For: The analysis of 17-hydroxyprogesterone (17-OHPG) is 1 of the 3 analytes along with cortisol and androstenedione, that constitutes the best screening test for congenital adrenal hyperplasia (CAH), caused by either 11- or 21-hydroxylase deficiency. Analysis for 17-OHPG is also useful as part of a battery of tests to evaluate females with hirsutism or infertility; both can result from adult-onset CAH

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and ideally also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment
modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels of up to 100 ng/dL are usually regarded as acceptable. See Steroid Pathways in Special Instructions.

**Reference Values:**

**Children**
- Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL.
- Term infants
  - 0-28 days: <630 ng/dL
  - Levels fall from newborn (<630 ng/dL) to prepubertal gradually within 6 months.
  - Prepubertal males: <110 ng/dL
  - Prepubertal females: <100 ng/dL
- Adults
  - Males: <220 ng/dL
  - Females
    - Follicular: <80 ng/dL
    - Luteal: <285 ng/dL
    - Postmenopausal: <51 ng/dL


**Clinical References:**

**GLIOF 35272**

**1p/19q Deletion in Gliomas, FISH, Tissue**

**Clinical Information:** Astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. It has been shown that specific genetic alterations are highly associated with specific morphologic types of gliomas. In addition, specific genetic alterations seem to predict prognosis (survival), as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology. Deletions of the short arm of chromosome 1(1p) and long arm of chromosome 19 (19q), are strongly correlated with gliomas of oligodendroglial morphology. Approximately 70%, 50%, and 50% of oligodendrogliomas have deletions of 19q, 1p, and of both 19q and 1p, respectively. Combined 1p and 19q loss is infrequent in gliomas of astrocytic origin. Thus, the presence of combined 1p/19q loss is strongly suggestive that a glioma is of oligodendrogloma lineage. Gains of chromosome 19 and of the 19 q-arm are associated with gliomas of astrocytic origin. Deletions of 1p and of both 1p and 19q also have been associated with response to various chemotherapeutic and radiotherapeutic regimens. These responses have been especially associated with high-grade oligodendrogliomas (anaplastic oligodendrogliomas). Chromosomal microarray (CMAPT / Chromosomal Microarray, Tumor, FFPE), rather than FISH, may be of benefit to evaluate for acquired alterations associated with the molecular classification of glioma.(1) See Cytogenetic Analysis of Glioma in Special Instructions.
Useful For: Aids in diagnosing oligodendroglioma tumors and predicting the response of an oligodendroglioma to therapy. May be useful in tumors with a complex "hybrid" morphology requiring differentiation from pure astrocytomas to support the presence of oligodendroglial differentiation/lineage. Indicated when a diagnosis of oligodendroglioma, both low-grade World Health Organization (WHO, grade II) and anaplastic (WHO, grade III) is rendered. Strongly recommended when a diagnosis of mixed oligoastrocytoma is rendered.

Interpretation: The presence of 1p deletion and combined 1p and 19q deletion supports a diagnosis of oligodendroglioma. The presence of gain of chromosome 19 supports a diagnosis of high-grade astrocytoma (glioblastoma multiforme). A negative result does not exclude a diagnosis of oligodendroglioma or high-grade astrocytoma.

Reference Values: An interpretive report will be provided.

Clinical Information: Erythrocytosis (ie, increased RBC mass, elevated RBC count, and elevated hemoglobin and hematocrit) may be primary, due to an intrinsic defect of bone marrow stem cells, as in polycythemia vera (PV); or secondary, in response to increased serum erythropoietin (Epo) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanism may be suspected. Unlike PV, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A rare subset of cases is associated with pheochromocytoma and paraganglioma formation later in life. Hereditary erythrocytosis may be caused by mutations in one of several genes and inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although de novo mutations have also been reported. Genetic mutations causing hereditary erythrocytosis have been found in genes coding for alpha and beta hemoglobins, hemoglobin stabilization proteins (eg, 2,3-bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF, prolyl hydroxylase domain: PHD, and von Hippel Lindau: VHL), see table. High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of mutations causing hereditary erythrocytosis is unknown. Table. Erythrocytosis Testing Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Markedly Increased Normal Useful For: Diagnosis of 2,3-bisphosphoglycerate mutase deficiency in individuals with lifelong, unexplained erythrocytosis Identifying mutation carriers in family members of an affected individual for the purposes of preconception genetic counseling Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

Reference Values:
An interpretive report will be provided.

Organization diagnostic criteria for SM require the presence of elevated mast cell counts on a bone
marrow biopsy and 1 of the following minor criteria: abnormal mast cell morphology, KIT Asp816Val
mutation, CD25-positive mast cells, or serum tryptase >20 ng/mL. Alternatively, SM diagnosis can be
made with the presence of 3 minor criteria in the absence of abnormal bone marrow studies. Measurement
of mast cell mediators in blood or urine is less invasive and is advised for the initial evaluation of
suspected cases. Elevated levels of serum tryptase, urinary N-methylhistamine (NMH),
2,3-dinor-11beta-prostaglandin F2 alpha (2,3 BPG), or leukotriene E4 (LTE4) are consistent with the
diagnosis of systemic mast cell disease.

**Useful For:** Screening for mast cell activation disorders including systemic mastocytosis

**Interpretation:** Elevated urine 2,3-dinor-11beta-prostaglandin F2 alpha is consistent with systemic
mastocytosis.

**Reference Values:**
<5,205 pg/mg creatinine

**Clinical References:**
Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence
Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood
pp 1537-1551

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**OH21**

**21-Hydroxylase Antibodies, Serum**

**Clinical Information:** Chronic primary adrenal insufficiency (Addison disease) is most commonly
caused by the insidious autoimmune destruction of the adrenal cortex and is characterized by the presence
of adrenal cortex autoantibodies in the serum. It can occur sporadically or in combination with other
autoimmune endocrine diseases, that together comprise Type I or Type II autoimmune polyglandular
syndrome (APS). The microsomal autoantigen 21-hydroxylase (55 kilodalton) has been shown to be the
primary autoantigen associated with autoimmune Addison disease. 21-Hydroxylase antibodies are
markers of autoimmune Addison disease, whether it presents alone, or as part of Type I or Type II (APS).

**Useful For:** Investigation of adrenal insufficiency Aid in the detection of those at risk of developing
autoimmune adrenal failure in the future

**Interpretation:** Positive results (> or =1 U/mL) indicate the presence of adrenal autoantibodies
consistent with Addison disease.

**Reference Values:**
<1 U/mL
Reference values apply to all ages.

**Clinical References:**
treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med 2014

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**CYPPS**

**21-Hydroxylase Gene (CYP21A2), Full Gene Analysis**

**Clinical Information:** Congenital adrenal hyperplasia (CAH), with an incidence rate of 1 in 10,000 to
18,000 live births, is one of the most common inherited syndromes. The condition is characterized by
impaired cortisol production due to inherited defects in steroid biosynthesis. The clinical consequences of
CAH, besides diminished cortisol production, depend on which enzyme is affected and whether the loss
of function is partial or complete. In >90% of CAH cases, the affected enzyme is 21-steroid hydroxylase, encoded by the CYP21A2 gene located on chromosome 6 within the highly recombinant human histocompatibility complex locus. Since sex steroid production pathways branch off proximal to this enzymatic step, affected individuals will have increased sex steroid levels. If there is some residual enzyme activity, a nonclassical phenotype results, with variable degrees of masculinization starting in later childhood or adolescence. On the other end of the spectrum are patients with complete loss of 21-hydroxylase function. This leads to both cortisol and mineral corticosteroid deficiency and is rapidly fatal if untreated due to loss of vascular tone and salt wasting. Because of its high incidence rate, 21-hydroxylase deficiency is screened for in most US newborn screening programs, typically by measuring 17-hydroxyprogesterone concentrations in blood spots by immunoassay. Confirmation by other testing strategies (eg, LC-MS/MS, CAHBS / Congenital Adrenal Hyperplasia [CAH] Newborn Screening, Blood Spot), or retesting after several weeks, is required for most positive screens because of the high false-positive rates of the immunoassays (due to physiological elevations of 17-hydroxyprogesterone in premature babies and immunoassay cross-reactivity with other steroids). In a small percentage of cases, additional testing will fail to provide a definitive diagnosis. In addition, screening strategies can miss many nonclassical cases, which may present later in childhood or adolescence and require more extensive steroid hormone profiling, including testing before and after adrenal stimulation with adrenocorticotropic hormone (ACTH)-1-24. For these reasons, genetic diagnosis plays an important ancillary role in both classical and nonclassical cases. In addition, the high carrier frequency (approximately 1 in 50) for CYP21A2 mutations makes genetic diagnosis important for genetic counseling. Genetic testing can also play a role in prenatal diagnosis of 21-hydroxylase deficiency. However, accurate genetic diagnosis continues to be a challenge because most of the mutations arise from recombination events between CYP21A2 and its highly homologous pseudogene, CYP21A1P (transcriptionally inactive). In particular, partial or complex rearrangements (with or without accompanying gene duplication events), which lead to reciprocal exchanges between gene and pseudogene, can present severe diagnostic challenges. Comprehensive genetic testing strategies must therefore allow accurate assessment of most, or all, known rearrangements and mutations, as well as unequivocal determination of whether the observed changes are located within a potentially transcriptionally active genetic segment. Testing of additional family members is often needed for clarification of genetic test results.

**Useful For:** Carrier screening and diagnosis of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH) as follow-up to positive CAH newborn screens and/or measurement of basal and adrenocorticotropic hormone (ACTH)-1-24 stimulated 17-hydroxyprogesterone, androstenedione, and other adrenal steroid levels. May be used to identify CYP21A2 mutations in individuals with a suspected diagnosis of 21-hydroxylase deficient CAH when a common mutation panel is negative or only identifies 1 mutation.

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
Clinical Information: Congenital adrenal hyperplasia (CAH), with an incidence rate of 1 in 10,000 to 18,000 live births, is one of the most common inherited syndromes. The condition is characterized by impaired cortisol production due to inherited defects in steroid biosynthesis. The clinical consequences of CAH, besides diminished cortisol production, depend on which enzyme is affected and whether the loss of function is partial or complete. In >90% of CAH cases, the affected enzyme is 21-steroid hydroxylase, encoded by the CYP21A2 gene located on chromosome 6 within the highly recombinant human histocompatibility complex locus. Since sex steroid production pathways branch off proximal to this enzymatic step, affected individuals will have increased sex steroid levels, resulting in virilization of female infants. If there is some residual enzyme activity, a nonclassical phenotype results, with variable degrees of masculinization starting in later childhood or adolescence. On the other end of the severity spectrum are patients with complete loss of 21-hydroxylase function. This leads to both cortisol and mineral corticosteroid deficiency and is rapidly fatal if untreated due to loss of vascular tone and salt wasting. Because of its high incidence rate, 21-hydroxylase deficiency is screened for in most United States newborn screening programs, typically by measuring 17-hydroxyprogesterone concentrations in blood spots by immunoassay. Confirmation by other testing strategies (eg, LC-MS/MS, CAHBS / Congenital Adrenal Hyperplasia [CAH] Newborn Screening, Blood Spot), or retesting after several weeks, is required for most positive screens because of the high false-positive rates of the immunoassays (due to physiological elevations of 17-hydroxyprogesterone in premature babies and immunoassay cross-reactivity with other steroids). In a small percentage of cases, additional testing will fail to provide a definitive diagnosis. In addition, screening strategies can miss many nonclassical cases, which may present later in childhood or adolescence and require more extensive steroid hormone profiling, including testing before and after adrenal stimulation with adrenocorticotropic hormone (ACTH)-1-24. For these reasons, genetic diagnosis plays an important ancillary role in both classical and nonclassical cases. In addition, the high carrier frequency (approximately 1 in 50) for CYP21A2 mutations makes genetic diagnosis important for genetic counseling. Genetic testing plays a role in prenatal diagnosis of 21-hydroxylase deficiency. However, accurate genetic diagnosis continues to be a challenge because most of the mutations arise from recombination events between CYP21A2 and its highly homologous pseudogene, CYP21A1P (transcriptionally inactive). In particular, partial or complex rearrangements (with or without accompanying gene duplication events), which lead to reciprocal exchanges between gene and pseudogene, can present severe diagnostic challenges. Comprehensive genetic testing strategies must therefore allow accurate assessment of most, or all, known rearrangements and mutations, as well as unequivocal determination of whether the observed changes are located within a potentially transcriptionally active genetic segment. Testing of additional family members is often needed for clarification of genetic test results.

Useful For: Ambiguous genitalia detected on prenatal ultrasound, particularly when fetus is confirmed XX female by chromosome analysis Pregnancies at risk for 21-hydroxylase deficient congenital adrenal hyperplasia based on family history

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

**22q11.2 Deletion/Duplication, FISH**

**Clinical Information:** The 22q deletion syndrome and 22q duplication syndrome have overlapping phenotypes. Deletions of 22q are associated with DiGeorge and velocardiofacial syndrome. These syndromes are manifested by the presence of growth deficiency, global developmental delay, heart defect, and hearing loss. The major birth defects include palatal clefting or insufficiency and thymus aplasia. Prominent facial features are widely spread eyes, superior placement of eyebrows, downward slanting palpebral fissures with or without ptosis (droopy upper eyelid), mild micrognathia (small jaw), and a long, narrow face. FISH studies are highly specific and do not exclude other chromosome abnormalities. For this reason, we recommend that patients suspected of having 22q deletion or duplication syndrome also have conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood) performed to rule out other chromosome abnormalities. The 22q deletion syndrome and 22q duplication syndrome have overlapping phenotypes. Deletions of 22q are associated with DiGeorge and velocardiofacial syndrome. These syndromes are manifested by the presence of growth deficiency, global developmental delay, heart defect, and hearing loss. The major birth defects include palatal clefting or insufficiency and thymus aplasia. Prominent facial features are widely spread eyes, superior placement of eyebrows, downward slanting palpebral fissures with or without ptosis (droopy upper eyelid), mild micrognathia (small jaw), and a long, narrow face. FISH studies are highly specific and do not exclude other chromosome abnormalities. For this reason, we recommend that patients suspected of having 22q deletion or duplication syndrome also have conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood) performed to rule out other chromosome abnormalities or translocations.

**Useful For:** Establishing a diagnosis of 22q deletion/duplication syndromes Detecting cryptic rearrangements involving 22q11.2 or 22q11.3 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern in each metaphase is considered negative for this probe. Any patient with a FISH signal pattern indicating loss of the critical region (1 signal) will be reported as having a deletion of the region tested by this probe. This is consistent with a diagnosis of 22q deletion syndrome. Any patient with a FISH signal pattern indicating duplication of the critical region (3 signals) will be reported as having a duplication of the region tested by this probe. This is consistent with a diagnosis 22q duplication syndrome.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

**25-Hydroxyvitamin D2 and D3, Serum**

**Clinical Information:** 25-Hydroxyvitamin D2 and D3 (25-OH-VitD) are steroid hormones that require 1-alpha-hydroxylation before expressing biological activity. Vitamin D compounds are derived from dietary ergocalciferol (from plants, VitD2) or cholecalciferol (from animals, VitD3), or by conversion of 7-dihydrocholesterol to VitD3 in the skin upon ultraviolet exposure. VitD2 and VitD3 are subsequently 25-hydroxylated in the liver to 25-OH-VitD. 25-OH-VitD represents the main body reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. A fraction of circulating 25-OH-VitD is converted to its active metabolites 1,25-dihydroxy vitamin D2 and D3 (1,25-OH-VitD), mainly by the kidneys. This process is regulated by parathyroid hormone (PTH), which increases 1,25-OH-VitD synthesis at the expense of the alternative, biologically inactive hydroxylation product 24,25-OH-VitD. Like other steroid hormones, 1,25-OH-VitD
binds to a nuclear receptor, influencing gene transcription patterns in target organs. 1,25-OH-VitD plays a primary role in the maintenance of calcium homeostasis. It promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the parathyroid glands is down-regulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, 1,25-OH-VitD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs. The exact 25-OH-VitD level reflecting optimal body stores remains unknown. Mild-to-moderate deficiency can be associated with osteoporosis or secondary hyperparathyroidism. Severe deficiency may lead to failure to mineralize newly formed osteoid in bone, resulting in rickets in children and osteomalacia in adults. The consequences of vitamin D deficiency on organs other than bone are not fully known, but may include increased susceptibility to infections, muscular discomfort, and an increased risk of colon, breast, and prostate cancer. Modest 25-OH-VitD deficiency is common; in institutionalized elderly, its prevalence may be >50%. Although much less common, severe deficiency is not rare either. Reasons for suboptimal 25-OH-VitD levels include lack of sunshine exposure, a particular problem in Northern latitudes during winter; inadequate intake; malabsorption (eg, due to Celiac disease); depressed hepatic vitamin D 25-hydroxylase activity, secondary to advanced liver disease; and enzyme-inducing drugs, in particular many antiepileptic drugs, including phenytoin, phenobarbital, and carbamazepine, that increase 25-OH-VitD metabolism. In contrast to the high prevalence of 25-OH-VitD deficiency, hypervitaminosis D is rare, and is only seen after prolonged exposure to extremely high doses of vitamin D. When it occurs, it can result in severe hypercalcemia and hyperphosphatemia.

**Useful For:** Diagnosis of vitamin D deficiency Differential diagnosis of causes of rickets and osteomalacia Monitoring vitamin D replacement therapy Diagnosis of hypervitaminosis D

**Interpretation:** Based on animal studies and large human epidemiological studies, 25-hydroxyvitamin D2 and D3 (25-OH-VitD) <25 ng/mL are associated with an increased risk of secondary hyperparathyroidism, reduced bone mineral density, and fractures, particularly in the elderly. Intervention studies support this clinical cutoff, showing a reduction of fracture risk with 25-OH-VitD replacement. Levels <10 ng/mL may be associated with more severe abnormalities and can lead to inadequate mineralization of newly formed osteoid, resulting in rickets in children and osteomalacia in adults. In these individuals, serum calcium levels may be marginally low, and parathyroid hormone (PTH) and serum alkaline phosphatase are usually elevated. Definitive diagnosis rests on the typical radiographic findings or bone biopsy/histomorphometry. Baseline biochemical work-up of suspected cases of rickets and osteomalacia should include measurement of serum calcium, phosphorus, PTH, and 25-OH-VitD. In patients where testing is not completely consistent with the suspected diagnosis, in particular if serum 25-OH-VitD levels are >10 ng/mL, an alternative cause for impaired mineralization should be considered. Possible differential diagnosis includes: partly treated vitamin D deficiency, extremely poor calcium intake, vitamin D resistant rickets, renal failure, renal tubular mineral loss with or without renal tubular acidosis, hypophosphatemic disorders (eg, X-linked or autosomal dominant hypophosphatemic rickets), congenital hypoparathyroidism, activating calcium sensing receptor mutations, and osteopetrosis. Measurement of serum urea, creatinine, magnesium, and 1,25-OH-VitD is recommended as a minimal additional work-up for these patients. 25-OH-VitD replacement in the United States typically consists of VitD2. Lack of clinical improvement and no reduction in PTH or alkaline phosphatase may indicate patient noncompliance, malabsorption, resistance to 25-OH-VitD, or additional factors contributing to the clinical disease. Measurement of serum 25-OH-VitD levels can assist in further evaluation, in particular as the liquid chromatography-tandem mass spectrometry methodology allows separate measurement of 25-OH-VitD3 and of 25-OH-VitD2, which is derived entirely from dietary sources or supplements. Patients who present with hypercalcemia, hyperphosphatemia, and low PTH may suffer either from ectopic, unregulated conversion of 25-OH-VitD to 1,25-OH-VitD, as can occur in granulomatous diseases, particular sarcoid, or from nutritionally-induced hypervitaminosis D. Serum 1,25-OH-VitD levels will be high in both groups, but only patients with hypervitaminosis D will have serum 25-OH-VitD concentrations of >80 ng/mL, typically >150 ng/mL.

**Reference Values:**

TOTAL 25-HYDROXYVITAMIN D2 AND D3 (25-OH-VitD)

<10 ng/mL (severe deficiency)*

10-19 ng/mL (mild to moderate deficiency)**
20-50 ng/mL (optimum levels)***  
51-80 ng/mL (increased risk of hypercalciuria)****  
>80 ng/mL (toxicity possible)*****  
*Could be associated with osteomalacia or rickets  
**May be associated with increased risk of osteoporosis or secondary hyperparathyroidism  
***Optimum levels in the healthy population; patients with bone disease may benefit from higher levels within this range  
****Sustained levels >50 ng/mL 25OH-VitD along with prolonged calcium supplementation may lead to hypercalciuria and decreased renal function  
*****80 ng/mL is the lowest reported level associated with toxicity in patients without primary hyperparathyroidism who have normal renal function. Most patients with toxicity have levels >150 ng/mL. Patients with renal failure can have very high 25-OH-VitD levels without any signs of toxicity, as renal conversion to the active hormone 1,25-OH-VitD is impaired or absent.  

These reference ranges represent clinical decision values, based on the 2011 Institute of Medicine report, that apply to males and females of all ages, rather than population-based reference values. Population reference ranges for 25-OH-VitD vary widely depending on ethnic background, age, geographic location of the studied populations, and the sampling season. Population-based ranges correlate poorly with serum 25-OH-VitD concentrations that are associated with biologically and clinically relevant vitamin D effects and are therefore of limited clinical value.


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**F5NUL**  
5'Nucleotidase  
Reference Values:  
0 - 15 U/L

**MTHAC**  
5,10-Methylenetetrahydrofolate Reductase A1298C, Mutation, Blood

**Clinical Information:** Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique MTHFR mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for one or more of these mutations. A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosine to thymine mutation.
at nucleotide position 677 (C677>T), encoding for an alanine-223 to valine substitution (MTHFR C677T). A second mutation in MTHFR exon 7, A1298C, results in a conversion of a glutamic acid codon to an alanine codon. The MTHFR A1298C reduces MTHFR activity to a lesser extent than C677T, but compound heterozygous A1298C/C677T may develop hyperhomocysteinemia. For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

**Useful For:** Direct mutation analysis for the MTHFR A1298C mutation should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism, who have increased basal homocysteine levels or an abnormal methionine-load test.

**Interpretation:** The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous MTHFR A1298C, homozygous MTHFR A1298C).

**Reference Values:**

Negative

**Clinical References:**


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**MTHP**

**61367**

**5,10-Methylenetetrahydrofolate Reductase C677T and A1298C Mutations, Blood**

**Clinical Information:** Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique MTHFR mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for 1 or more of these mutations. A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosome to thymine mutation at nucleotide position 677, encoding for an alanine-223 to valine substitution (MTHFR C677T). A second mutation in MTHFR exon 7, A1298C, results in a conversion of a glutamic acid codon to an alanine codon. The MTHFR A1298C mutation reduces MTHFR activity to a lesser extent than C677T, but compound heterozygous MTHFR A1298C/C677T may develop hyperhomocysteinemia. For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

**Useful For:** Direct mutation analysis for the MTHFR C677T and/or A1298C mutations should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test.
Interpretation: The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous MTHFR C677T, homozygous MTHFR C677T; negative, heterozygous MTHFR A1298C, homozygous MTHFR A1298C).

Reference Values:
Negative


MTHFR 81648

5,10-Methylenetetrahydrofolate Reductase C677T, Mutation, Blood

Clinical Information: Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique MTHFR mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for 1 or more of these mutations. A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosine to thymine mutation at nucleotide position 677 (C677->T), encoding for an alanine-223 to valine substitution (MTHFR C677T). Patients who are homozygous for the MTHFR C677T mutation may develop hyperhomocysteinemia, especially with concurrent deficiency of vitamins B12, B6 (pyridoxine), or folic acid. This mutation is quite common, with a carrier frequency of 31% to 39% (homozygote frequency 9%-17%) among the white North American population. The MTHFR C677T mutation test is a direct assay of patient leukocyte genomic DNA. For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

Useful For: Direct mutation analysis for the MTHFR C677T mutation should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test.

Interpretation: The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous MTHFR C677T, homozygous MTHFR C677T).

Reference Values:
Negative
**Clinical References:**

---

**FLUC 82741**

**5-Flucytosine, Serum**

**Clinical Information:** Flucytosine is a broad-spectrum antifungal agent generally used in combined therapy (often with amphotericin B) for treatment of fungal infections such as cryptococcal meningitis. Concerns with toxicity (bone marrow suppression, hepatic dysfunction) and development of fungal resistance limit use of flucytosine, particularly as a monotherapy. The drug is well-absorbed orally, but can also be administered intravenously (available outside of the United States). There is good correlation between serum concentrations of flucytosine with both efficacy and risk for toxicity. Because of the drug's short half-life (3-6 hours), therapeutic monitoring is typically performed at peak levels, 1 to 2 hours after an oral dose or 30 minutes after intravenous administration. Flucytosine is eliminated primarily as unmetabolized drug in urine. Patients with renal dysfunction may require dose adjustments or more frequent monitoring to ensure that serum concentrations do not accumulate to excessive levels. Nephrotoxicity associated with use of amphotericin B can affect elimination of flucytosine when the drugs are coadministered.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity May be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to flucytosine when peak serum levels (1-2 hours after oral dosing) are >25.0 mcg/mL. Some infections may require higher concentrations for efficacy. Toxicity is more likely when peak serum concentrations are >100.0 mcg/mL.

**Reference Values:**
Therapeutic concentration:
- Peak >25.0 mcg/mL (difficult infections may require higher concentrations)
- Toxic concentration:
  - Peak >100.0 mcg/mL

**Clinical References:**

---

**F5HAR 57333**

**5-HIAA (5-Hydroxyindoleacetic Acid), Random Urine**

**Reference Values:**

<table>
<thead>
<tr>
<th>5-HIAA mg/g creat</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10 YRS: 12.0 or less</td>
</tr>
<tr>
<td>&gt;10 YRS: 10.0 or less</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Creatinine, Random Urine mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mg/dL</td>
</tr>
<tr>
<td>0-6 Months 2-32</td>
</tr>
<tr>
<td>7-11 Months 2-36</td>
</tr>
<tr>
<td>1-2 Years 2-128</td>
</tr>
<tr>
<td>3-8 Years 2-149</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 35
**5-Hydroxyindoleacetic Acid (5-HIAA), 24 Hour, Urine**

**Clinical Information:** 5-Hydroxyindoleacetic acid (5-HIAA) is the major metabolite of serotonin and is excreted in the urine. Intestinal carcinoid tumors along with neuroendocrine tumors can produce excess amounts of 5-HIAA and serotonin especially in individuals with carcinoid syndrome. Carcinoid syndrome is characterized by carcinoid tumors, flushing, heart disease, and hepatomegaly. Measurement of 5-HIAA in a 24-hour urine specimen can diagnose carcinoid disease with a high specificity.

**Useful For:** Biochemical diagnosis and monitoring of intestinal carcinoid syndrome

**Interpretation:** Elevated excretion of 5-hydroxyindoleacetic acid is a probable indicator of the presence of a serotonin-producing tumor, if pharmacological and dietary artifacts have been ruled out.

**Reference Values:**
< or =8 mg/24 hours

**Clinical References:**

---

**5-Methyltetrahydrofolate**

**Reference Values:**
5-Methyltetrahydrofolate

<table>
<thead>
<tr>
<th>Age</th>
<th>5MTHF (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>40-240</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>40-240</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>40-187</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>40-150</td>
</tr>
<tr>
<td>5.0-10</td>
<td>40-128</td>
</tr>
<tr>
<td>10-15</td>
<td>40-120</td>
</tr>
<tr>
<td>Adults</td>
<td>40-120</td>
</tr>
</tbody>
</table>

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

**DISCLAIMER** required by the FDA for high complexity clinical laboratories: HPLC testing was developed and its performance characteristics determined by Medical Neurogenetics. These HPLC tests have not been cleared or approved by the U.S. FDA.
**Custody, Meconium**

**Clinical Information:** Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though it is used elsewhere for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of the first acetyl converts heroin into 6-monoacetylmorphine (6-MAM).(2,3) Heroin is rarely found in meconium since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of heroin use. Like heroin, 6-MAM has a very short half-life; however, its detection time in meconium, the first fecal material passed by the neonate, is uncharacterized. 6-MAM is further metabolized into morphine, the dominant metabolite of heroin, and morphine will typically be found in a specimen containing 6-MAM. Opiates, including heroin, have been shown to readily cross the placenta and distribute widely into many fetal tissues.(4) Opiate use by the mother during pregnancy increased the risk of prematurity and being small for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared with methadone-exposed infants. Heroin-exposed infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome.(5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(6) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(7) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(6) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain-of-custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of 6-monoacetylmorphine (6-MAM) in meconium is definitive for heroin use by the mother. However, the absence of 6-MAM does not rule-out heroin use, because of its short half-life.

**Reference Values:**
- **Negative**
- **Positives are reported with a quantitative LC-MS/MS result.**
- **Cutoff concentration:**
  - 6-MAM by LC-MS/MS: 5 ng/g

**Clinical References:**
7. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG: Meconium passage in utero mechanisms, consequences, and management. Obstet...
**Clinical Information:** Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though elsewhere it is used for rapid relief of pain. Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system. Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin. Heroin is rarely found intact in urine, since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window.

**Useful For:** Determination of heroin use

**Interpretation:** The presence of 6-monoacetylmorphine (6-MAM) in urine is definitive for recent heroin use. However, the absence of 6-MAM does not rule-out heroin use because of its short half-life. 6-MAM is typically only detectable within 24 hours of heroin use. 6-MAM is further metabolized into morphine, which may be detected 1 to 2 days after 6-MAM is no longer measurable. Morphine will typically be found in a specimen containing 6-MAM.

**Reference Values:**
- **Negative**
- **Cutoff concentrations:**
  - 6-MAM: <5 ng/mL

**Clinical References:**

---

**Clinical Information:** Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though elsewhere it is used for rapid relief of pain. Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system. Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin. Heroin is rarely found intact in urine, since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Determination of heroin use Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen.
at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of 6-monoacetylmorphine (6-MAM) in urine is definitive for recent heroin use. However, the absence of 6-MAM does not rule out heroin use because of its short half-life. 6-MAM is typically only detectable within 24 hours of heroin use. 6-MAM is further metabolized into morphine, which may be detected 1 to 2 days after 6-MAM is no longer measurable. Morphine will typically be found in a specimen containing 6-MAM.(2,3)

**Reference Values:**

<table>
<thead>
<tr>
<th>Cutoff Concentration</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MAM</td>
<td>ng/mL</td>
</tr>
<tr>
<td>&lt;5</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical References:**

---

**6-Monoacetylmorphine (6-MAM), Confirmation, Meconium**

**Clinical Information:** Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though it is used elsewhere for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of the first acetyl converts heroin into 6-monoacetylmorphine (6-MAM).(2,3) Heroin is rarely found in meconium since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of heroin use. Like heroin, 6-MAM has a very short half-life; however, its detection time in meconium, the first fecal material passed by the neonate, is uncharacterized. 6-MAM is further metabolized into morphine, the dominant metabolite of heroin, and morphine will typically be found in a specimen containing 6-MAM. Opiates, including heroin, have been shown to readily cross the placenta and distribute widely into many fetal tissues.(4) Opiate use by the mother during pregnancy increased the risk of prematurity and being small for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared with methadone-exposed infants. Heroin-exposed infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome.(5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(6) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(7) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(6)

**Useful For:** Detection of in utero drug exposure up to 5 months before birth

**Interpretation:** The presence of 6-monoacetylmorphine (6-MAM) in meconium is definitive for heroin use by the mother. However, the absence of 6-MAM does not rule-out heroin use, because of its short half-life.

**Reference Values:**

<table>
<thead>
<tr>
<th>Cutoff Concentration</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positives</td>
<td>mg/mL</td>
</tr>
</tbody>
</table>

Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentration:
6-MAM by LC-MS/MS: 5 ng/g


F68KD

68kD (hsp-70)

Interpretation: Antibodies to inner ear antigen (68kD) occur in approximately 70% of patients with autoimmune hearing loss. The antibody tests to this 68kD antigen parallel with disease activity. In addition, a majority of patients positive for antibodies to 68kd are responsive to corticosteroid treatment. (Hirose et al: The Laryngoscope 109:1769 – 1999)

Reference Values:
Qualitative test â€“ Positive or Negative

ACAC

Acacia, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalsants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
ACANT 80401

Acanthamoeba/Naegleria species, Corneal Scraping or Spinal Fluid

Clinical Information: The free-living amebae are ubiquitous in the environment, and may be found in soil and fresh water sources. Naegleria fowleri may enter the central nervous system (CNS) during exposure to infected water and cause a fulminant meningitis in previously healthy individuals. In contrast, Acanthamoeba species and Balamuthis mandrillaris cause chronic granulomatous encephalitis in immunocompromised (and, rarely, immunocompetent) adults, and typically disseminate to the CNS from a primary lung or skin source. Acanthamoeba species can also cause a painful keratitis when organisms are introduced into the eye. This typically occurs during contact lens use when the lenses or storage or cleaning solutions are contaminated. Amebae can also enter the cornea with abrasion or trauma. Amebic keratitis can cause blindness if untreated. Most cases respond to treatment once a diagnosis is made, but some cases prove to be resistant to therapy with no antimicrobials uniformly active against the organisms.

Useful For: Diagnosis of Acanthamoeba species and Naegleria fowleri, in central nervous system or ocular specimens

Interpretation: Organisms seen on stains of the original specimen smear or growth on culture media are positive tests.

Reference Values:

EYE
Negative for Acanthamoeba species

CENTRAL NERVOUS SYSTEM
Negative for Acanthamoeba/Naegleria species

Clinical References:

ACAR 82850

Acarus siro, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class I or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
<td></td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FACET**

**Acetaminophen (Tylenol, Datril), Urine**

**Reference Values:**

Units: ug/mL

Note: Analysis performed on urine.
Reference ranges have not been established for urine specimens.

**ACMA**

**Acetaminophen, Serum**

**Clinical Information:** Acetaminophen (found in Anacin-3, Comtrex, Contac, Datril, Dristan, Excedrin, Nyquil, Sinutab, Tempera, TYLENOL, Vanquish, and many others) is an analgesic, antipyretic drug lacking significant anti-inflammatory activity. It is metabolized by the liver with a normal elimination half-life of <4 hours. In normal therapeutic doses, a minor metabolite, possessing electrophilic alkylating activity, readily reacts with glutathione in the liver to yield a detoxified product. In overdose situations, liver glutathione is consumed and the toxic metabolite (postulated metabolite: benzoquinone) reacts with cellular proteins resulting in hepatotoxicity, characterized by centrilobular necrosis, and possible death, if untreated. N-acetylcysteine can substitute for glutathione and serves as an antidote. Serum concentration and half-life are the only way to assess degree of intoxication in early stages since other liver function studies (eg, bilirubin, liver function enzymes) will not show clinically significant increases until after tissue damage has occurred, at which point therapy is ineffective.

**Useful For:** Monitoring toxicity in overdose cases
**Interpretation:** Therapeutic concentration: <30 mcg/mL Normal half-life: <4 hours Toxic concentration: >150 mcg/mL Toxic half-life: >4 hours The toxic level is dependent on half-life. When the half-life is 4 hours, hepatotoxicity generally will not occur unless the concentration is >150 mcg/mL. The level at which toxicity occurs decreases with increasing half-life until it is encountered at values as low as 50 mcg/mL when the half-life reaches 12 hours. For half-life determination, draw 2 specimens at least 4 hours apart and note the exact time of each draw. Half-life can be calculated from the concentrations and the time interval.

**Reference Values:**
Therapeutic: <30 mcg/mL
Toxic: >150 mcg/mL 4 hours after dose


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**ASNES**

**Acetate Non-Specific Esterase Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

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**FACTO**

**Acetoacetate, Serum or Plasma**

**Reference Values:**
Reporting limit determined each analysis.

Acetoacetate
Normal range for adults: 5-30 mcg/mL

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**ARBI**

**Acetylcholine Receptor (Muscle AChR) Binding Antibody, Serum**

**Clinical Information:** Myasthenia gravis (MG) is characterized by weakness and easy fatigability that are relieved by rest and anticholinesterase drugs. The weakness in most cases results from an autoantibody-mediated loss of functional acetylcholine receptors (AChR) in the postsynaptic membrane of skeletal muscle. Demonstration of muscle AChR autoantibodies in a patient's serum supports the diagnosis of acquired (autoimmune) MG, and quantitation provides a baseline for future comparisons. Muscle AChR antibodies are not found in congenital forms of MG and are uncommon in neurologic conditions other than acquired MG, with the exception of patients with paraneoplastic autoimmune neurological disorders, and Lambert-Eaton myasthenic syndrome (LES) with or without cancer (13% of LES patients have positive results for muscle AChR binding or striational antibodies). Patients with autoimmune liver disease are also frequently seropositive. The assay for muscle AChR binding antibodies is considered a first-order test for the laboratory diagnosis of MG, and for detecting "subclinical MG" in recipients of D-penicillamine, in patients with thymoma without clinical evidence of MG, and in patients with graft-versus-host disease.

**Useful For:** Confirming the diagnosis of myasthenia gravis (MG) Distinguishing acquired disease (90% positive) from congenital disease (negative) Detecting subclinical MG in patients with thymoma or graft-versus-host disease Monitoring disease progression in MG or response to immunotherapy An adjunct to the test for P/Q-type calcium channel binding antibodies as a diagnostic aid for Lambert-Eaton myasthenic syndrome (LES) or primary lung carcinoma

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Current as of July 8, 2016 11:28 am CDT
**Interpretation:** Values >0.02 nmol/L are consistent with a diagnosis of acquired myasthenia gravis (MG), provided that clinical/electrophysiological criteria support that diagnosis. The assay for muscle acetylcholine receptor (AChR) binding antibodies is positive in approximately 90% of nonimmunosuppressed patients with generalized MG. The frequency of antibody detection is lower in MG patients with weakness clinically restricted to ocular muscles (71%), and antibody titers are generally low in ocular MG (eg, 0.03-1.0 nmol/L). Results may be negative in the first 12 months after symptoms of MG appear or during immunosuppressant therapy. Note: In follow up of seronegative patients with adult-acquired generalized MG, 17.4% seroconvert to positive at 12 months (ie, seronegativity rate at 12 months is 8.4%). Thirty eight percent of persistently seronegative patients have muscle-specific kinase (MuSK) antibody. Sera of nonmyasthenic subjects bind per liter 0.02 nmol or less of muscle AChR complexed with (125)I-labeled-alpha-bungarotoxin. In general, there is not a close correlation between antibody titer and severity of weakness, but in individual patients, clinical improvement is usually accompanied by a decrease in titer.

**Reference Values:**
< or =0.02 nmol/L


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**ACHE_9287**

**Acetylcholinesterase, Amniotic Fluid (AChE-AF), Amniotic Fluid**

**Clinical Information:** Neural tube defects (NTD) are a type of birth defect involving openings along the brain and spine. They develop in the early embryonic period when the neural tube fails to completely close. NTD can vary widely in severity. Anencephaly represents the most severe end of the spectrum and occurs when the cranial end fails to form, resulting in an absence of the forebrain, the area of the skull that covers the brain, and the skin. Most infants with anencephaly are stillborn or die shortly after birth. NTD along the spine are referred to as spina bifida. Individuals with spina bifida may experience hydrocephalus, urinary and bowel dysfunction, club foot, lower body weakness, and loss of feeling or paralysis. Severity varies depending upon whether the NTD is covered by skin, whether herniation of the meninges and spinal cord are present, and the location of the lesion. NTD not covered by skin are referred to as open NTD and are typically more severe than closed NTD. Likewise those presenting with herniation and higher on the spinal column are typically more severe. Most NTD occur as isolated birth defects with an incidence of approximately 1 in 1,000 to 2 in 1,000 live births in the United States. Rates vary by geographic region with lower rates being observed in the North and West than the South and East. A fetus is at higher risk when the pregnancy is complicated by maternal diabetes, exposed to certain anticonvulsants, or there is a family history of NTD. Studies have shown a dramatic decrease in risk as a result of maternal dietary supplementation with folic acid. The March of Dimes currently recommends that all women of childbearing age take 400 micrograms of folic acid daily, increasing the amount to 600 mg/day during pregnancy. For women who have had a prior pregnancy affected by an NTD, the recommended dose is at least 4,000 mg/day starting at least 1 month preconception and continuing through the first trimester. When an NTD is suspected based upon maternal serum alpha-fetoprotein (AFP) screening results or diagnosed via ultrasound, analysis of AFP and acetylcholinesterase (AChE) in amniotic fluid are useful diagnostic tools. AChE is primarily active in the central nervous system with small amounts of enzyme found in erythrocytes, skeletal muscle, and fetal serum. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of an open NTD.

**Useful For:** Diagnosing open neural tube defects, and to a lesser degree, ventral wall defects

**Interpretation:** The presence of acetylcholinesterase in amniotic fluid is consistent with open neural tube defects and, to a lesser degree, ventral wall defects.

**Reference Values:**
Negative (reported as negative [normal] or positive [abnormal] for inhibitable acetylcholinesterase)

Reference values were established in conjunction with alpha-fetoprotein testing and include only
amniotic fluids from pregnancies between 14 and 21 weeks gestation.


ACS H

Acetylcholinesterase, Erythrocytes

Clinical Information: Acetylcholinesterase (AChE) is anchored to the external surface of the RBC. Its appearance in a lysate of red cells is diminished in paroxysmal nocturnal hemoglobinuria (PNH). The use of red cell AChE for PNH has not gained widespread acceptance, and flow cytometry testing is most often used for PNH (see PANH/81156 PI-Linked Antigen, Blood). Red cell AChE is most often used to detect past exposure to organophosphate insecticides with resultant inhibition of the enzyme. Both the pseudocholinesterase activity in serum and red cell AChE are inhibited by these insecticides, but they are dramatically different vis-a-vis the temporal aspect of the exposure. The half-life of the pseudo-enzyme in serum is about 8 days, and the "true" cholinesterase (AChE) of red cells is over 3 months (determined by erythropoietic activity). Recent exposure up to several weeks is determined by assay of the pseudo-enzyme and months after exposure by measurement of the red cell enzyme. The effect of the specific insecticides may be important to know prior to testing.

Useful For: Detecting effects of remote (months) past exposure to cholinesterase inhibitors (organophosphate insecticide poisoning)

Interpretation: Activities less than normal are suspect for exposure to certain insecticides.

Reference Values:
31.2-61.3 U/g of hemoglobin


GAABS

Acid Alpha-Glucosidase, Blood Spot

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme alpha-glucosidase (GAA) leading to an accumulation of glycogen in the lysosome causing swelling, cell damage, and progressive organ dysfunction. Pompe disease is caused by mutations in the GAA gene, and it is characterized by muscle hypotonia, weakness, cardiomyopathy, and eventually death due to either cardiorespiratory or respiratory failure. The clinical phenotype, in general, appears to be dependent on residual enzyme activity, with complete loss of activity causing onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms are characterized by later onset and longer survival. The estimated incidence is 1 in 40,000 live births. Enzyme replacement therapy (ERT) improves outcome in many patients with either classic infantile onset or later onset forms of Pompe disease. Early initiation of treatment improves the prognosis and makes early diagnosis of Pompe disease desirable. Because of this, newborn screening for Pompe disease has recently been implemented in some states. The early identification and treatment of infants with Pompe disease has been shown to be helpful in reducing the morbidity and mortality associated with this disease. Since Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, in particular the juvenile and adult-onset forms, is often considered late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Testing traditionally required a skin or muscle biopsy to establish cultures for enzyme testing. More recently, molecular genetic testing of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis) became clinically available. Determination of the enzyme activity in dried blood spot specimens can be performed in a timely fashion and provide better guidance in the decision to submit samples for further confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis).

Useful For: Evaluation of patients of any age with a clinical presentation suggestive of Pompe disease
Interpretation: Normal results (>0.5 nmol/h/mL) in properly submitted specimens are not consistent with classic Pompe disease. Affected individuals typically show < or =0.5 nmol/h/mL; however, some later onset cases may show higher enzyme activity. Results < or =0.5 nmol/h/mL can be followed up by molecular genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis) to determine carrier, pseudodeficiency, or disease status.

Reference Values:
Normal >0.5 nmol/mL/h


ACPHS

Acid Phosphatase Stain (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

SAFB

Acid-Fast Smear for Mycobacterium

Clinical Information: Mycobacterium tuberculosis is a leading infectious disease cause of death worldwide. The Centers for Disease Control and Prevention has reported a rise in the incidence of tuberculosis associated with AIDS, foreign-born cases, and increased transmission in high-risk populations. There has also been a rise in the number of Mycobacterium tuberculosis strains that exhibit resistance to 1 or more antituberculosis drugs. The public health implications of these facts are considerable. Because Mycobacterium tuberculosis is readily spread by airborne particles, rapid diagnosis and isolation of infected persons is important. Nontuberculous mycobacteria infections also cause significant morbidity and mortality in humans, particularly in immunocompromised persons. Detection of acid-fast bacilli in sputum specimens allows rapid identification of individuals who are likely to be infected with mycobacteria while definitive diagnosis and treatment are pursued.

Useful For: Detection of acid-fast bacilli in clinical specimens

Interpretation: Patients whose sputum specimens are identified as acid-fast positive should be considered potentially infected with Mycobacterium tuberculosis, pending definitive diagnosis by molecular methods or mycobacterial culture.

Reference Values:
Negative (reported as positive or negative)

### Actinomyces Culture

**Clinical Information:** Anaerobic Actinomyces are nonsporeforming, thin branching, gram-positive bacilli that are part of the normal flora of the human oral cavity and may also colonize the gastrointestinal and female genital tracts. Their presence is important in preserving the usual bacterial populations of the mouth and in preventing infection with pathogenic bacteria. Actinomyces are generally of low pathogenicity but may be an important factor in the development of periodontal disease and may cause soft tissue infections in colonized areas of the body following trauma (surgical or otherwise). The typical lesion consists of an outer zone of granulation around central purulent loculations containing masses of tangled organisms ("sulfur granule"). Chronic burrowing sinus tracts develop. Typical actinomycotic infections occur around the head and neck, in the lung and chest wall, and in the peritoneal cavity and abdominal wall. Actinomycosis of the female genital tract occurs in association with use of intrauterine contraceptive devices. Purulent collections containing "sulfur granules" may drain from some sinus tracts opening to the skin.

**Useful For:** Diagnosing anaerobic Actinomyces involved in infections

**Interpretation:** Isolation of anaerobic Actinomyces in significant numbers from well collected specimens including blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with the identified organism.

**Reference Values:**
- No growth
- Identification of probable pathogens

**Clinical References:**

### Activated Partial Thromboplastin Time (APTT), Plasma

**Clinical Information:** The activated partial thromboplastin time (APTT) test reflects the activities of most of the coagulation factors, including factor XII and other "contact factors" (prekallikrein [PK] and high-molecular-weight kininogen [HMWK]) and factors XI, IX, and VIII in the intrinsic procoagulant pathway, as well as coagulation factors in the common procoagulant pathway that include factors X, V, II and fibrinogen (factor I). The APTT also depends on phospholipid (a partial thromboplastin) and ionic calcium, as well as an activator of the contact factors (eg, silica), but reflects neither the extrinsic procoagulant pathway that includes factor VII and tissue factor, nor the activity of factor XIII (fibrin stabilizing factor). The APTT is variably sensitive to the presence of specific and nonspecific inhibitors of the intrinsic and common coagulation pathways, including lupus anticoagulants or antiphospholipid antibodies. Lupus anticoagulants may interfere with in vitro phospholipid-dependent coagulation tests, such as the APTT, and prolong the clotting time. Lupus anticoagulants are antibodies directed towards neoepitopes presented by complexes of phospholipid and proteins, such as prothrombin (factor II) or beta 2 glycoprotein I, but these antibodies do not specifically inhibit any of the coagulation factors. Clinically, lupus anticoagulant represents an important marker of thrombotic tendency. In contrast, patients with specific coagulation inhibitors, such as factor VIII inhibitor antibodies, have a significant risk of hemorrhage and often require specific treatment for effective management. Both types of disorders may have similar prolongation of the APTT.

**Useful For:** Monitoring heparin therapy (unfractionated heparin) Screening for certain coagulation factor deficiencies Detection of coagulation inhibitors such as lupus anticoagulant, specific factor inhibitors, and nonspecific inhibitors
**Interpretation:** Since activated partial thromboplastin time (APTT) reagents can vary greatly in their sensitivity to unfractionated heparin (UFH), it is important for laboratories to establish a relationship between APTT response and heparin concentration. The therapeutic APTT range in seconds should correspond with an UFH concentration of 0.3 to 0.7 U/mL as assessed by heparin assay (inhibition of factor Xa activity with detection by a chromogenic substrate). In our laboratory, we have found the therapeutic APTT range to be approximately 70 to 120 seconds. Prolongation of the APTT can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a nonspecific inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. Shortening of the APTT usually reflects either elevation of factor VIII activity in vivo that most often occurs in association with acute or chronic illness or inflammation, or spurious results associated with either difficult venipuncture and specimen collection or suboptimal specimen processing.

**Reference Values:**
28-38 seconds

**Clinical References:**

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**APCRV**

**Activated Protein C Resistance V (APCRV), Plasma**

**Clinical Information:** Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight=62,000 da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC interacts with and proteolyses factors V/Va and VIII/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time clotting test fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have a specific point mutation in the procoagulant factor V gene (1691G-A, factor V Leiden) encoding for a glutamine (Q) substitution for arginine (R)-506 in the heavy chain of factor V (factor V R506Q). This amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden mutation varies depending on the population. Approximately 5% of asymptomatic white Americans of non-Hispanic ancestry are heterozygous carriers, while the carrier frequency among African Americans, Asian Americans, and Native Americans is <1%, and the carrier frequency for Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among whites of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common, but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with homozygosity or homozygosity for the factor V Leiden mutation; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

**Useful For:** Evaluation of patients with incident or recurrent venous thromboembolism (VTE)
Evaluation of individuals with a family history of VTE Evaluation of women with recurrent miscarriage or complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) Possibly useful for evaluation of individuals with a history of arterial thrombosis (eg, stroke, acute myocardial infarction, or other acute coronary syndromes), especially among young
patients (ie, <50 years) or patients with no other risk factors for arthrosclerosis

**Interpretation:** An activated protein C (APC)-R ratio of <2.3 suggests abnormal resistance to APC of hereditary origin. DNA-based testing for the factor V Leiden mutation (F5DNA / Factor V Leiden [R506Q] Mutation, Blood) may be helpful in confirming or excluding hereditary APC-resistance, after initial screening with the APC-resistance test.

**Reference Values:**

**APCRV RATIO**

\[ > \text{ or } =2.3 \]

Pediatric reference range has neither been established nor is available in scientific literature. The adult reference range likely would be applicable to children >6 months.

**REPORTABLE RANGE**

1.0-10.0

**Clinical References:**


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**Acute Hepatitis Profile**

**Clinical Information:** Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of the viral hepatitis in United States adults. HAV infection is spread by the oral/fecal route and produces acute hepatitis which follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and in institutions or high density centers such as prisons and health care centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products, eg, blood transfusion, sharing of needles by drug addicts. The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these chronic carriers are asymptomatic, others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. See Advances in the Laboratory Diagnosis of Hepatitis C (2002) in Publications, and HBV Infection-Diagnostic Approach and Management Algorithm and Testing Algorithm for the Diagnosis of Hepatitis C in Special Instructions.

**Useful For:** The differential diagnosis of recent acute viral hepatitis

**Interpretation:** Hepatitis A: Antibody against hepatitis A antigen is usually detectable by the onset of symptoms (usually 15-45 days after exposure). The initial antibody consists almost entirely of IgM subclass antibody. Antibody to hepatitis A virus (anti-HAV) IgM usually falls to undetectable levels 3 to 6 months after infection. Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Hepatitis B surface antibody (anti-HBs)
appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as
the immune response following a course of inoculation with the hepatitis B vaccine. Initially, hepatitis B
core antibody (anti-HBc) consists almost entirely of the IgM subclass. Anti-HBc, IgM can be detected
shortly after the onset of symptoms and is usually present for 6 months. Anti-HBc may be the only marker
of a recent HBV infection detectable following the disappearance of HBsAg, and prior to the appearance
of anti-HBs, ie, window period. Hepatitis C: Hepatitis C antibody is usually not detectable during the
early months following infection and is almost always detectable by the late convalescent stage of
infection. Hepatitis C antibody is not neutralizing and does not provide immunity. If HBsAg, anti-HAV
(IgM), and anti-HCV are negative and patient's condition warrants, consider testing for Epstein-Barr virus
or cytomegalovirus. See Advances in the Laboratory Diagnosis of Hepatitis C (2002) in Publications, and
HBV Infection-Diagnostic Approach and Management Algorithm and Testing Algorithm for the
Diagnosis of Hepatitis C in Special Instructions.

Reference Values:
HEPATITIS B SURFACE ANTIGEN
Negative

HEPATITIS B CORE ANTIBODY, IgM
Negative

HEPATITIS A IgM ANTIBODY
Negative

HEPATITIS C ANTIBODY SCREEN
Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.

Clinical References: 1. Lemon SM: Type A viral hepatitis: epidemiology, diagnosis, and

Acute Myeloid Leukemia (AML), FISH

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias,
with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia
and accounts for the majority of infant (<1 year old) leukemia. Several subtypes of AML have been
recognized (termed AML-M0, M1, M2, M3, M4, M5, M6, and M7) based on the cell morphology and
myeloid lineage involved. In addition to morphology, several recurrent chromosomal abnormalities have
been linked to specific subtypes of AML. The most common chromosome abnormalities associated with
AML include t(8;21), t(15;17), inv(16), +8, t(6;9), t(8;16), t(1;22), t(9;22), (3;5) and abnormalities of the
MLL gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML
include AFF1- t(4;11), MLTT4- t(6;11), MLLT3- t(9;11), MLLT10- t(10;11), CREBBP- t(11;16), ELL-
t(11;19p13.1), and MLLT1- t(11;19p13.3). AML can also evolve from myelodysplasia (MDS). Thus, the
common chromosome abnormalities associated with MDS can also be identified in AML, which include:
inv(3), -5/5q-, 7q-, +8, 13q-, 17p-, 20q-, t(1;3), and t(3;21). In combination, the multiple recurrent
chromosome abnormalities identified in patients with AML are observed in approximately 60% of
diagnostic AML cases. Conventional chromosome analysis is the gold standard for identification of the
common, recurrent chromosome abnormalities in AML however some of the subtle rearrangements can
be missed (eg, inv[16] and MLL abnormalities). FISH analysis of nonproliferating (interphase) cells can
be used to detect the common chromosome abnormalities observed in patients with AML. The
abnormalities have diagnostic and prognostic relevance and this testing can also be used to track response
to therapy.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen
in patients with acute myeloid leukemia or other myeloid malignancies Evaluating specimens in which
standard cytogenetic analysis is unsuccessful. Identifying and tracking known chromosome abnormalities in patients with myeloid malignancies and tracking response to therapy

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an acute myeloid leukemia of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Acute Porphyria, Multi-Gene Panel**

**Clinical Information:** Acute porphyria is caused by autosomal dominant mutations in 1 of 3 genes: HMBS, associated with acute intermittent porphyria (AIP); CPOX, associated with hereditary coproporphyria (HCP); and PPOX, associated with variegate porphyria (VP). Mutations in these genes show incomplete penetrance, and patients with a confirmed deleterious mutation may be asymptomatic. Clinical manifestations of acute porphyria include attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropsychiatric symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HCP and VP are also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in establishing a diagnosis of acute porphyria.

**Useful For:** Confirmation of acute porphyria for patients with clinical features of the disease

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Acyclovir, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

**Synonym(s):** Zovirax
Usual therapeutic range (vs. Genital Herpes) during chronic oral daily divided dosages of 1200 – 2400 mg:

- Peak: 0.40 – 2.0 mcg/mL plasma
- Trough: 0.14 – 1.2 mcg/mL plasma

**ACRN 82413**

**Acylcarnitines, Quantitative, Plasma**

**Clinical Information:** Acylcarnitine analysis enables the diagnosis of many disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs. Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry (MS/MS). Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and/or failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common viral infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor/vitamin supplementation. Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. Disorders Detectable by Acylcarnitine Analysis:

- Fatty Acid Oxidation Disorders: Short-chain acyl-CoA dehydrogenase (SCAD) deficiency - Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency - Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency - Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency & trifunctional protein deficiency - Very long-chain acyl-CoA dehydrogenase (VLCHAD) deficiency - Carnitine palmitoyl transferase type II (CPT-II) deficiency - Carnitine-acylcarnitine translocase (CACT) deficiency - Electron transfer flavoprotein (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency [MADD]; glutaric acidemia type II) - Organic Acid Disorders: - Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) - Propionic Acidemia - Methylmalonic Acidemia - Isovaleric Acidemia - 3-hydroxy-3-methylglutaryl-CoA carboxylase deficiency - 3-Methylcrotonyl-CoA carboxylase deficiency - Biotinidase deficiency - Multiple carboxylase deficiency - Isobutyryl-CoA dehydrogenase deficiency - 2-Methylbutyryl-CoA dehydrogenase deficiency - Beta-ketothiolase deficiency - Malonic aciduria - Ethylmalonic encephalopathy *Further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than 1 condition.

**Useful For:** Diagnosis of fatty acid oxidation disorders and several organic acidurias Evaluating treatment during follow-up of patients with fatty acid beta-oxidation disorders and several organic acidurias

**Interpretation:** An interpretive report is provided. The individual quantitative results support the interpretation of the acylcarnitine profile but are not diagnostic by themselves. The interpretation is based on pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required. For information on the follow-up of specific acylcarnitine elevations, see Special Instructions for the following algorithms:

- Newborn Screening Follow-up for Elevations of C8, C6, and C10 Acylcarnitines (also applies to any plasma C8, C6, and C10 acylcarnitine elevations)
- Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma C4 acylcarnitine elevation)
- Newborn Screening Follow-up for Elevations of C8, C6, and C10 Acylcarnitines (also applies to any plasma C8, C6, and C10 acylcarnitine elevations)
Follow-up for Isolated C5 Acylcarnitine Elevations (also applies to any plasma C5 acylcarnitine elevation)

**Reference Values:**

<table>
<thead>
<tr>
<th>Acylcarnitine</th>
<th>&lt; 7 days (nmol/mL)</th>
<th>7-8 years (nmol/mL)</th>
<th>≥ 8 years (nmol/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcarnitine, C2</td>
<td>2.14-15.89</td>
<td>2.00-27.57</td>
<td>2.00-17.83</td>
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<tr>
<td>Acrylylcarnitine, C3:1</td>
<td></td>
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<tr>
<td>Propionylcarnitine, C3</td>
<td></td>
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<tr>
<td>Formiminoglutamate, FIGLU</td>
<td></td>
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<tr>
<td>Iso-/Butyrylcarnitine, C4</td>
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<tr>
<td>Tiglylcarnitine, C5:1</td>
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<tr>
<td>Isovaleryl-/2-Methylbutyrylcam C5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-OH-iso-/butyrylcarnitine, C4-OH</td>
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<tr>
<td>Hexenoylcarnitine, C6:1</td>
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<tr>
<td>Hexanoylcarnitine, C6</td>
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<tr>
<td>3-OH-isovalerylcarnitine, C5-OH</td>
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<tr>
<td>Benzoylcarnitine</td>
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<td>Heptanoylcarnitine, C7</td>
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<tr>
<td>3-OH-hexanoylcaritnine, C6-OH</td>
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<tr>
<td>Phenylacetylcarnitine</td>
<td></td>
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<tr>
<td>Salicylcarnitine</td>
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<tr>
<td>Octenoylcarnitine, C8:1</td>
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<tr>
<td>Octanoylcarnitine, C8</td>
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</tr>
<tr>
<td>Malonylcarnitine, C3-DC</td>
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<tr>
<td>Decadienoylcaritnine, C10:2</td>
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<tr>
<td>Decenoylcarnitine, C10:1</td>
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<tr>
<td>Decanoylcarnitine, C10</td>
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<tr>
<td>Methylmalonyl-/succinylcarn, C4-DC</td>
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<tr>
<td>3-OH-decenoylcaritnine, C10:1-OH</td>
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<tr>
<td>Glutarylcaritnine, C5-DC</td>
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<td>Dodecenoylcaritnine, C12:1</td>
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<tr>
<td>Dodecanoylcaritnine, C12</td>
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<td>3-Methylglutarylcaritnine, C6-DC</td>
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<tr>
<td>3-OH-dodecenoylcaritnine, C12:1-OH</td>
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<tr>
<td>3-OH-dodecanoylcaritnine, C12-OH</td>
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<tr>
<td>Tetradecadienoylcaritnine, C14:2</td>
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<tr>
<td>Tetradecenoylcaritnine, C14:1</td>
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<tr>
<td>Tetradecanoylcaritnine, C14</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Octanediolcaritnine, C8-DC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3-OH-tetradecenoylcaritnine C14:1OH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3-OH-tetradecanoylcarnitine, C14-OH
Hexadecenoylcarnitine, C16:1
Hexadecanoylcarnitine, C16
3-OH-hexadecenoylcarnitine, C16:1-OH
3-OH-hexadecanoylcarnitine, C16-OH
Octadecadienoylcarnitine, C18:2
Octadecenoylcarnitine, C18:1
Octadecanoylcarnitine, C18
Dodecanedioylcarnitine, C12-DC
3-OH-octadecadienoylcarnitine, C18:2-OH
3-OH-octadecenoylcarnitine, C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH


ACLYLG 81249

Acylglycines, Quantitative, Urine

Clinical Information: Acylglycines are glycine conjugates of acyl-CoA species. Acylglycines are normal intermediates of amino acid and fatty acid metabolism; however, in abnormal concentrations acylglycines are biochemical markers of selected inborn errors of metabolism (IEM). Analysis of acylglycines is a useful screening test in the evaluation of patients with a suspected IEM, though additional studies are necessary to establish a diagnosis. The biochemical diagnosis of these disorders is a complex process achieved by multiple tests and their integrated interpretation. Although acylglycines are often ordered in conjunction with organic acids, acylglycine analysis is more sensitive and specific for the identification of asymptomatic patients and those with mild and/or intermittent biochemical phenotypes that could be missed by organic acid analysis alone. The quantitative analysis of urinary acylglycines is particularly effective for identifying asymptomatic patients affected with disorders including: -Short chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency -Glutaric acidemia type II -Ethylmalonic encephalopathy -2-Methylbutyryl-CoA dehydrogenase deficiency -Isovaleryl-CoA dehydrogenase deficiency -Glutaryl-CoA dehydrogenase deficiency

Useful For: Biochemical screening of asymptomatic patients affected with 1 of the following inborn errors of metabolism: -Short chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency -Glutaric acidemia type II -Ethylmalonic encephalopathy -2-Methylbutyryl-CoA dehydrogenase deficiency -Isovaleryl-CoA dehydrogenase deficiency -Glutaryl-CoA dehydrogenase deficiency

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance; a correlation to available clinical information; elements of differential diagnosis; recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis); name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere; and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
### Control Values Results Expressed as mg/g Creatinine

<table>
<thead>
<tr>
<th>Compound</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylmalonic Acid</td>
<td>0.5-20.2</td>
</tr>
<tr>
<td>2-Methylsuccinic Acid</td>
<td>0.4-13.8</td>
</tr>
<tr>
<td>Glutaric Acid</td>
<td>0.6-15.2</td>
</tr>
<tr>
<td>Isobutyrylglycine</td>
<td>0.00-11.0</td>
</tr>
<tr>
<td>n-Butyrylglycine</td>
<td>0.1-2.1</td>
</tr>
<tr>
<td>2-Methylbutyrylglycine</td>
<td>0.3-7.5</td>
</tr>
<tr>
<td>Isovalerylglycine</td>
<td>0.3-14.3</td>
</tr>
<tr>
<td>n-Hexanoylglycine</td>
<td>0.2-1.9</td>
</tr>
<tr>
<td>n-Octanoylglycine</td>
<td>0.1-2.1</td>
</tr>
<tr>
<td>3-Phenylpropionylglycine</td>
<td>0.00-1.1</td>
</tr>
<tr>
<td>Suberylglcine</td>
<td>0.00-11.0</td>
</tr>
<tr>
<td>trans-Cinnamoylglycine</td>
<td>0.2-14.7</td>
</tr>
<tr>
<td>Dodecanedioic Acid (12 DCA)</td>
<td>0.00-1.1</td>
</tr>
<tr>
<td>Tetradecanedioic Acid (14 DCA)</td>
<td>0.00-1.0</td>
</tr>
<tr>
<td>Hexadecanedioic Acid (16 DCA)</td>
<td>0.00-1.0</td>
</tr>
</tbody>
</table>

### Clinical References:

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### FAAAB 58031

**Adalimumab Concentration and Anti-Adalimumab Antibody**

**Reference Values:**

- **Adalimumab Drug Level**
  - Quantitation Limit: <0.6 ug/mL
  - Results of 0.6 or higher indicated detection of adalimumab

  In the presence of anti-adalimumab antibodies, they adalimumab drug level reflects the antibody-unbound fraction of adalimumab concentration in serum.

- **Anti-Adalimumab Antibody**
  - Quantitation Limit: <25 ng/mL
  - Results of 25 or higher indicates detection of anti-adalimumab antibodies.

**Test Performed by:** Esoterix Endocrinology
4301 Lost Hills Road
Calabasas Hills, CA 91301

### ADM13 ADAMTS13 Activity and Inhibitor Profile

Current as of July 8, 2016 11:28 am CDT
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Clinical Information:** Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy (TMA) syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and renal dysfunction. The large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy, and in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome), but far more commonly is acquired. Acquired TTP may be considered to be primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP, clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay.

**Useful For:** Assisting with the diagnosis of congenital or acquired thrombotic thrombocytopenic purpura

**Reference Values:**

- **ADAMTS13 ACTIVITY ASSAY**
  - \( \geq 70\% \)

- **ADAMTS13 INHIBITOR SCREEN**
  - Negative

- **ADAMTS13 BETHESDA TITER**
  - \(<0.4\) BU


**ADMBU 61214**

**ADAMTS13 Inhibitor Bethesda Titer**

**Reference Values:**

- \(<0.4\) BU

  This is not an orderable test.
  Only orderable as part of a profile. For more information see ADM13 / ADAMTS13 Activity and Inhibitor Profile.

**Clinical References:**

**ADMS 61213**

**ADAMTS13 Inhibitor Screen Assay**

**Reference Values:**

- Negative

  This is not an orderable test.
  Only orderable as part of a profile. For more information see ADM13 / ADAMTS13 Activity and
Inhibitor Profile.

**ADSTM 62206**  
**Additional Flow Stimulant (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**FADDB 57876**  
**Adenosine Deaminase, Blood**  
**Reference Values:**  
0.3 - 1.4 IU/g Hb

**FADDC 58029**  
**Adenosine Deaminase, CSF**  
**Reference Values:**  
0.0 – 1.5 U/L

**FADPC 75004**  
**Adenosine Deaminase, Pericardial Fluid**  
**Reference Values:**  
0.0 – 11.3 U/L

**FADPT 75003**  
**Adenosine Deaminase, Peritoneal Fluid**  
**Reference Values:**  
0.0 – 7.3 U/L

**FADPL 75002**  
**Adenosine Deaminase, Pleural Fluid**  
**Reference Values:**  
0.0 – 9.4 U/L

**FADV 91728**  
**Adenovirus Antibody, Serum**  
**Reference Values:**  
Reference Range: <1:8

**Interpretive Criteria:**  
- <1:8: Antibody Not Detected  
- >or= 1:8: Antibody Detected

Single titers of >or= 1:64 are indicative of recent or current infection. Titters of 1:8 â€“ 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis.

**FAAST 57116**  
**Adenovirus Antigen Detection, Gastroenteritis, EIA**  
**Reference Values:**
A positive test result in association with diarrhea highly suggests that Adenovirus is the cause of the gastroenteritis. Adenovirus may shed asymptomatically up to 18 months after infection. The virus may also become latent, then reactivate. If the patient, in fact, has a bacterial enterocolitis due to Staphylococcus aureus, high levels of the bacterial protein A may cross-react with this test and result in a false positive.

**FADE**

Adenovirus DNA, Quantitative Real-Time PCR

**Reference Values:**

CONDITION:  
REFERENCE RANGE:  <500 copies/mL

**LADV**

Adenovirus, Molecular Detection, PCR

**Clinical Information:** Human adenoviruses cause a variety of diseases including pneumonia, cystitis, conjunctivitis, diarrhea, hepatitis, myocarditis, and encephalitis. In humans, adenoviruses have been recovered from almost every organ system. Infections can occur at any time of the year and in all age groups. Currently, there are 51 adenovirus serotypes that have been grouped into 6 separate subgenera. Culture is the gold standard for the diagnosis for adenovirus infection. However, it can take up to 3 weeks to achieve culture results (Mayo Clinic’s shell vial culture provides more rapid results, reported at 2 and 5 days). Serological tests have faster turnaround times, but can be less sensitive compared to culture. PCR offers a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.

**Useful For:** Aiding in the diagnosis of adenovirus infections

**Interpretation:** A positive result indicates the presence of adenoviruses. A negative result does not rule out the presence of adenoviruses because organisms may be present at levels below the detection limits of this assay.

**Reference Values:**

NEGATIVE


**LCADP**

Adenovirus, Molecular Detection, PCR, Plasma

**Clinical Information:** Human adenoviruses cause a variety of diseases including pneumonia, cystitis, conjunctivitis, diarrhea, hepatitis, myocarditis, and encephalitis. In humans, adenoviruses have been recovered from almost every organ system. Infections can occur at any time of the year and in all age groups. Currently, there are 51 adenovirus serotypes that have been grouped into 6 separate subgenera. Culture is the gold standard for the diagnosis for adenovirus infection; however, it can take up to 3 weeks to achieve culture results (Mayo’s shell vial culture provides more rapid results, reported at 2 and 5 days). PCR offers a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.
Useful For: An aid in diagnosing adenovirus infections

Interpretation: A positive result indicates the presence of adenovirus nucleic acid. A negative result does not rule out the presence of adenoviruses because organisms may be present at levels below the detection limits of this assay.

Reference Values:
Negative


<table>
<thead>
<tr>
<th>FADIP 91378</th>
<th>Adiponectin</th>
</tr>
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<tbody>
<tr>
<td>Reference Values:</td>
<td></td>
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<tr>
<td>Reference Ranges for Adiponectin:</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Males (mcg/mL)</td>
</tr>
<tr>
<td>&lt;25 kg/meters-squared</td>
<td>4-26</td>
</tr>
<tr>
<td>25-30 kg/meters-squared</td>
<td>4-20</td>
</tr>
<tr>
<td>&gt;30 kg/meters-squared</td>
<td>2-20</td>
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</table>

<table>
<thead>
<tr>
<th>FADMK 91925</th>
<th>ADmark Phospho-Tau/Total-Tau/A Beta 42 CSF Analysis &amp; Interpretation (Symptomatic)</th>
</tr>
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<tbody>
<tr>
<td>Reference Values:</td>
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<td>A final report will be attached in MayoAccess.</td>
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<table>
<thead>
<tr>
<th>RACTH 82140</th>
<th>Adrenocorticotrophic Hormone, ACTH, IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).</td>
<td></td>
</tr>
<tr>
<td>Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to...</td>
<td></td>
</tr>
</tbody>
</table>
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>&gt; or ≥100</td>
<td></td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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### ACTH

**Adrenocorticotropic Hormone (ACTH), Plasma**

**Clinical Information:** Adrenocorticotropic hormone (ACTH), the primary stimulator of adrenal cortisol production, is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH), which is released by the hypothalamus. Plasma ACTH and cortisol levels exhibit peaks (6-8 a.m.) and nadirs (11 p.m.). Cortisol, the main glucocorticoid, plays a central role in glucose metabolism and in the body's response to stress. Only a small percentage of circulating cortisol is biologically active (free form), with the majority of cortisol inactive (protein bound). Cortisol is inactivated in the liver and excreted in the urine as conjugated compounds (largely 17-hydroxysteroids). Urine free cortisol levels reflect circulating free plasma cortisol levels. Disorders of cortisol production: Hypercortisolism -Cushing syndrome: - Cushing disease (pituitary ACTH-producing tumor) - Ectopic ACTH-producing tumor - Ectopic CRH - Adrenal cortisol-producing tumor - Adrenal hyperplasia (non-ACTH dependent, autonomous cortisol-producing adrenal nodules) Hypocortisolism -Addison disease-primary adrenal insufficiency -Secondary adrenal insufficiency -Pituitary insufficiency -Hypothalamic insufficiency -Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

**Useful For:** Determining the cause of hypercortisolism and hypocortisolism

**Interpretation:** In a patient with hypocortisolism, an elevated adrenocorticotropic hormone (ACTH) indicates primary adrenal insufficiency, whereas a value that is not elevated is consistent with secondary adrenal insufficiency from a pituitary or hypothalamic cause. In a patient with hypercortisolism (Cushing syndrome), a suppressed value is consistent with a cortisol-producing adrenal adenoma or carcinoma, primary adrenal micronodular hyperplasia, or exogenous corticosteroid use. Normal or elevated ACTH in a patient with Cushing syndrome puts the patient in the ACTH-dependent Cushing syndrome category. This is due to either an ACTH-producing pituitary adenoma or ectopic production of ACTH (bronchial carcinoid, small cell lung cancer, others). Further diagnostic studies such as dexamethasone suppression testing, corticotropin-releasing hormone stimulation testing, petrosal sinus sampling, and imaging studies are usually necessary to define the ACTH source.

**Reference Values:**
10-60 pg/mL (a.m. draws)
No established reference values for p.m. draws
Pediatric reference values are the same as adults, as confirmed by peer reviewed literature.


**Adulterants Survey, Chain of Custody, Urine**

**Clinical Information:** Specimen adulteration is the manipulation of a sample that may cause falsely negative test results for the presence of drugs of abuse. Common adulterants that may affect testing are water, soap, bleach, vinegar, oxidants, and salt. The adulteration testing includes assessment of creatinine concentration, pH, urine specific gravity, presence or absence of an oxidant, and presence or absence of nitrite. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Assess the possible adulteration of a urine specimen submitted for drug of abuse testing, as well as for providing the urine creatinine for "creatinine normalization" This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** See Adulterant Survey Algorithm in Special Instructions.

**Reference Values:**
Cutoff concentrations
- Oxidants: 200 mg/L
- Nitrites: 500 mg/L

### Cutoff concentrations
- Oxidants: 200 mg/L
- Nitrites: 500 mg/L

### Aeroallergen Screen

**Interpretation:** Tree Mix 2 (Cottonwood, Elm, Maple, Oak, Pecan) IgE Class IgE (kU/L) Comment 0
- <0.10 Negative 0/1
- 0.10-0.34 Equivocal 1
- 0.35-0.69 Low Positive 2
- 0.70-3.4 Moderate Positive 3
- 3.5-17.4 High Positive 4
- 17.5-49.9 Very High Positive 5
- 50.0-99.9 Very High Positive 6
- > or = 100 Very High Positive

Regional Mix 2 (Altern, Cat, Dog, D. farinae, Horse) IgE Class IgE (kU/L) Comment 0
- <0.10 Negative 0/1
- 0.10-0.34 Equivocal 1
- 0.35-0.69 Low Positive 2
- 0.70-3.4 Moderate Positive 3
- 3.5-17.4 High Positive 4
- 17.5-49.9 Very High Positive 5
- 50.0-99.9 Very High Positive 6
- > or = 100 Very High Positive

**Reference Values:**

<table>
<thead>
<tr>
<th>Immunoglobulin E (IgE)</th>
<th>Reference Ranges (IU/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Related</td>
<td>Reference Range</td>
</tr>
<tr>
<td>1-11 months</td>
<td>0-12</td>
</tr>
<tr>
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</tr>
<tr>
<td>51-80 year</td>
<td>3-48</td>
</tr>
</tbody>
</table>

A 24 year old reference range is shown when no age is given.

Tree Mix 2 IgE
- <0.35 kU/L
  (Includes Cottonwood, Elm, Maple, Oak, Pecan)

Regional Mix 2 IgE*
- <0.35 kU/L
  (Includes Altern, Cat, Dog, D. farinae, Horse)

*This test was developed and its performance characteristics determined by Viracor-IBT Laboratories. It has not been cleared or approved by the FDA.

Regional Mix 3 IgE*
- <0.35 kU/L
  (Includes Bahia, Berm, EngPlan, Lb's Qtrs, Ragwd, Rye)

*This test was developed and its performance characteristics determined by Viracor-IBT Laboratories. It has not been cleared or approved by the FDA.

### Aerobe Ident by Sequencing (Bill Only)

**Reference Values:**

This test is for billing purposes only. This is not an orderable test.
AGXTZ Gene, Full Gene Analysis

Clinical Information: Primary hyperoxaluria type 1 (PH1) is a hereditary disorder of glyoxylate metabolism caused by deficiency of alanine:glyoxylate-aminotransferase (AGT), a hepatic enzyme that converts glyoxylate to glycine. Absence of AGT activity results in conversion of glyoxylate to oxalate, which is not capable of being degraded. Therefore, excess oxalate is excreted in the urine, causing kidney stones (urolithiasis), nephrocalcinosis, and kidney failure. As kidney function declines, blood levels of oxalate increase markedly, and oxalate combines with calcium to form calcium oxalate deposits in the kidney, eyes, heart, bones, and other organs, resulting in systemic disease. Pyridoxine (vitamin B6), a cofactor of AGT, is effective in reducing urine oxalate excretion in some PH1 patients. Presenting symptoms of PH1 include nephrolithiasis, nephrocalcinosis, or end-stage kidney disease with or without a history of urolithiasis. Age of symptom onset is variable; however, most individuals present in childhood or adolescence with symptoms related to kidney stones. In some infants with a more severe phenotype, kidney failure may be the initial presenting feature. Less frequently, affected individuals present in adulthood with recurrent kidney stones or kidney failure. End-stage kidney disease is most often seen in the third decade of life, but can occur at any age. The exact prevalence and incidence of PH1 are not known, but prevalence rates of 1 to 3 per million population and incidences of 0.1 per million/year have been estimated from population surveys. Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, 24 Hour, Urine). Abnormal urinary excretion of oxalate is strongly suggestive of, but not diagnostic for, this disorder, as there are other forms of inherited (type 2 and non-PH1/PH2) hyperoxaluria and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycolate in the presence of hyperoxaluria is suggestive of PH1. Historically, the diagnosis of PH1 was confirmed by AGT enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases. PH1 is inherited as an autosomal recessive disorder caused by mutations in the AGXT gene, which encodes the enzyme AGT. Several common AGXT mutations have been identified including c.33dupC, p.Gly170Arg (c.508G->A), and p.Ile244Thr (c.731T->C). These mutations account for at least 1 of the 2 affected alleles in approximately 70% of individuals with PH1. Direct sequencing of the AGXT gene is predicted to identify 99% of alleles in individuals who are known by enzyme analysis to be affected with PH1. While age of onset and severity of disease is variable and not necessarily predictable by genotype, a correlation between pyridoxine responsiveness and homozygosity for the p.Gly170Arg mutation has been observed. (Note: testing for the p.Gly170Arg mutation only is available by ordering AGXTG / Alanine:Glyoxylylate Aminotransferase [AGXT] Mutation Analysis [G170R], Blood). Pyridoxine (vitamin B6) is a known cofactor of AGT and is effective in reducing urine oxalate excretion in some PH1 patients treated with pharmacologic doses. Individuals with 2 copies of the p.Gly170Arg mutation have been shown to normalize their urine oxalate when treated with pharmacologic doses of pyridoxine and those with a single copy of the mutation show reduction in urine oxalate. This is valuable because not all patients have been shown to be responsive to pyridoxine, and strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable.

Useful For: Confirming a diagnosis of primary hyperoxaluria type 1 Carrier testing for individuals with a family history of primary hyperoxaluria type 1 in the absence of known mutations in the family

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


ALT

Alanine Aminotransferase (ALT) (GPT), Serum

Clinical Information: Alanine aminotransferase (ALT) is present primarily in liver cells. In viral hepatitis and other forms of liver disease associated with hepatic necrosis, serum ALT is elevated even before the clinical signs and symptoms of the disease appear. Although serum levels of both aspartate aminotransferase (AST) and ALT become elevated whenever disease processes affect liver cell integrity, ALT is a more liver-specific enzyme. Serum elevations of ALT are rarely observed in conditions other than parenchymal liver disease. Moreover, the elevation of ALT activity persists longer than does AST activity.

Useful For: Diagnosis and monitoring of liver disease associated with hepatic necrosis

Interpretation: Elevated alanine aminotransferase (ALT) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least ten times above the normal range. Levels may reach values as high as one hundred times the upper reference limit, although twenty to fifty-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions affecting the liver, ALT is characteristically as high as or higher than aspartate aminotransferase (AST), and the ALT/AST ratio, which normally and in other condition is <1, becomes greater than unity. ALT levels are usually elevated before clinical signs and symptoms of disease appear.

Reference Values:
Males
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are <12 months of age.
Females
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are <12 months of age.


AGXTG

Alanine:Glyoxylate Aminotransferase (AGXT) Mutation Analysis (G170R), Blood

Clinical Information: Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disorder in which excessive oxalates are formed by the liver and excreted by the kidneys, causing a wide spectrum of disease ranging from renal failure in infancy to mere renal stones in late adulthood. It is caused by deficiencies of the liver-specific peroxisomal enzyme AGXT (alanine-glyoxylate amino-transferase). The diagnosis may be suspected when clinical signs, increased urinary oxalate, glycolate, and glycerate excretion are present. Diagnostic confirmation requires the enzyme assay of the liver tissue, although this test is not readily available. The toxicity of excess oxalate has been implicated in disease pathogenesis. Thus, treatment options have primarily centered on limiting oxalate ingestion and absorption. Pyridoxine (vitamin B[6]) has proven to be a promising therapeutic agent by increasing the concentration of cofactor involved in the metabolic reactions that decrease oxalate production. However, only 20% to 30% of patients have been known to be responsive to pyridoxine. Testing patients for pyridoxine responsiveness has been recommended at any stage of renal function, although assessment of pyridoxine responsiveness

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLabs.com
is not always easy to perform and diagnostic criteria have not been standardized. Recently, researchers at Mayo Clinic found that patients with a particular mutation (Gly170Arg) in the AGXT gene are responsive to the pyridoxine, while affected individuals without this mutation are not responsive.

**Useful For:** Identifying patients with the pyridoxine responsive form of primary hyperoxaluria type 1 (PH1) Determining the presence of the Gly170Arg (G170R) mutation in the AGXT gene Carrier testing of at-risk family members

**Interpretation:** Reported as negative or positive. The laboratory provides an interpretation of the results. This interpretation includes an overview of the results and their significance and a correlation to available clinical information.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FALUF 57286**
**Albumin, Body Fluid**

**Reference Values:**
Units: mg/dL
Not Established

**Clinical Information:** Albumin is a carbohydrate-free protein, which constitutes 55% to 65% of total plasma protein. It maintains oncotic plasma pressure, is involved in the transport and storage of a wide variety of ligands, and is a source of endogenous amino acids. Albumin binds and solubilizes various compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Hypoalbuminemia is caused by several factors: impaired synthesis due either to liver disease (primary) or due to diminished protein intake (secondary); increased catabolism as a result of tissue damage and inflammation; malabsorption of amino acids; and increased renal excretion (e.g., nephrotic syndrome).

**Useful For:** Plasma or serum levels of albumin are frequently used to assess nutritional status

**Interpretation:** Hyperalbuminemia is of little diagnostic significance except in the case of dehydration. When plasma or serum albumin values fall below 2.0 g/dL, edema is usually present.

**Reference Values:**
> or =12 months: 3.5-5.0 g/dL

Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

**ALB 8436**
**Albumin, Serum**

**Clinical Information:** Albumin is a carbohydrate-free protein, which constitutes 55% to 65% of total plasma protein. It maintains oncotic plasma pressure, is involved in the transport and storage of a wide variety of ligands, and is a source of endogenous amino acids. Albumin binds and solubilizes various compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Hypoalbuminemia is caused by several factors: impaired synthesis due either to liver disease (primary) or due to diminished protein intake (secondary); increased catabolism as a result of tissue damage and inflammation; malabsorption of amino acids; and increased renal excretion (e.g., nephrotic syndrome).

**Useful For:** Plasma or serum levels of albumin are frequently used to assess nutritional status

**Interpretation:** Hyperalbuminemia is of little diagnostic significance except in the case of dehydration. When plasma or serum albumin values fall below 2.0 g/dL, edema is usually present.

**Reference Values:**
> or =12 months: 3.5-5.0 g/dL

Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

**FALBU 90309**
**Albuterol, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis
Synonym(s): Proventil

Peak plasma levels following a single 4 mg oral solution: 18 ng/mL at 2.5 hours post dose.
Peak plasma levels following a single 0.04-0.1 mg inhaler dose: 0.6-1.4 ng/mL at 3-5 hours post dose.
Steady state trough plasma levels following a 2 mg (conventional tablet) every 6 hours regimen: 3.8 - 4.3 ng/mL.
Steady state trough plasma levels following a 4 mg (extended-release tablet) every 12 hours regimen: 3.0 - 4.8 ng/mL.
Steady state trough plasma levels following a 4 mg (conventional tablet) every 6 hours regimen: 7.8 - 12.0 ng/mL.

**FALCO 90084**  
**Alcohol, Methyl**  
**Reference Values:**  
Units: mg/dL  
Methanol (methyl alcohol) concentrations greater than 3 mg/dL are potentially toxic.

**ALD 82050**  
**Aldolase Stain (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.
Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**ALS 8363**  
**Aldolase, Serum**  
**Clinical Information:** Aldolase is necessary for glycolysis in muscle as a "rapid response" pathway for production of adenosine triphosphate, independent of tissue oxygen. Aldolase catalyses the conversion of fructose 1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, an important reaction in the glycolytic breakdown of glucose to lactate in muscle. Aldolase is a tetramer whose primary structure depends upon the tissue from which it was synthesized (liver, muscle, brain). The brain form of aldolase has, because of its preponderance in white cells, been suggested to be a leukemia marker, but this is not confirmed. Elevated values are found in muscle diseases, such as Duchenne muscular dystrophy, dermatomyositis, polymyositis, and limb-girdle dystrophy.

**Useful For:** Detection of muscle disease

**Interpretation:** The highest levels of aldolase are found in progressive (Duchenne) muscular dystrophy. Lesser elevations are found in dermatomyositis, polymyositis, and limb-girdle dystrophy. In dystrophic conditions causing hyperaldolasmia, the increase in aldolase becomes less dramatic as muscle mass decreases. Reference (normal) values are observed in polio, myasthenia gravis, and multiple sclerosis. Aldolase increases in myocardial infarction in a time pattern similar to the aspartate aminotransferase. Increases are also associated with acute viral hepatitis, but levels are normal or slightly elevated in chronic hepatitis, portal cirrhosis, and obstructive jaundice. Elevations may also be seen with gangrene, prostate tumors, trichinosis, some carcinomas metastatic to the liver, some chronic leukemias, some blood dyscrasias, and delirium tremens.

**Reference Values:**
0-16 years: <14.5 U/L  
> or =17 years: <7.7 U/L
**Aldosterone with Sodium, 24 Hour, Urine**

**Clinical Information:** Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone can stimulate aldosterone secretion. Urinary aldosterone levels are inversely correlated with urinary sodium excretion. Normal subjects will show a suppression of urinary aldosterone with adequate sodium repletion. Primary hyperaldosteronism, which may be caused by aldosterone-secreting adrenal adenoma/carcinomas or adrenal cortical hyperplasia, is characterized by hypertension accompanied by increased aldosterone levels, hypernatremia, and hypokalemia. Secondary hyperaldosteronism (eg, in response to renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) is characterized by increased aldosterone levels and increased plasma rennin activity.

**Useful For:** Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:** Under normal circumstances, if the 24-hour urinary sodium excretion is >200 mEq, the urinary aldosterone excretion should be <10 mcg/24 hours. Urinary aldosterone excretion >12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. 24-Hour urinary sodium excretion should exceed 200 mEq to document adequate sodium repletion. See Renin-Aldosterone Studies in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**

**ALDOSTERONE**
- 0-30 days: 0.7-11.0 mcg/24 hours*
- 1-11 months: 0.7-22.0 mcg/24 hours*
- > or =1 year: 2.0-20.0 mcg/24 hours


**SODIUM**
- 41-227 mmol/24 hours
- If the 24-hour urinary sodium excretion is >200 mmol, the urinary aldosterone excretion should be <10 mcg.

**Clinical References:**
aldosterone-secreting adrenal adenoma/carcinomas or adrenal cortical hyperplasia, is characterized by hypertension accompanied by increased aldosterone levels, hypernatremia, and hypokalemia. Secondary hyperaldosteronism (eg, in response to renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter's syndrome) is characterized by increased aldosterone levels and increased plasma rennin activity.

**Useful For:** Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:** Under normal circumstances, if the 24-hour urinary sodium excretion is >200 mEq, the urinary aldosterone excretion should be <10 mcg/24 hours. Urinary aldosterone excretion >12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. 24-Hour urinary sodium excretion should exceed 200 mEq to document adequate sodium repletion. See Renin-Aldosterone Studies in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
- 0-30 days: 0.7-11.0 mcg/24 hours*
- 31 days-11 months: 0.7-22.0 mcg/24 hours*
- > or =1 year: 2.0-20.0 mcg/24 hours


**Clinical References:**
3. Hurwitz S,

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**Aaldosterone, Inferior Vena Cava, Serum**

**Clinical Information:** Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondly, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

**Useful For:** Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:** A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio > or =20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
No established reference values.

**Clinical References:**
3. Hurwitz S,
Aldosterone, Left Adrenal Vein, Serum

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio > or =20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

Reference Values:
No established reference values.


Aldosterone, Right Adrenal Vein, Serum

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio > or =20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions.
Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
No established reference values.

**Clinical References:**

**Clinical Information:**
Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

**Useful For:**
Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:**
A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio ≥20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions.

**Reference Values:**
- 0-30 days: 17-154 ng/dL
- 31 days-11 months: 6.5-86 ng/dL
- 1-10 years:
  - < or =40 ng/dL (supine)
  - < or =124 ng/dL (upright)
- > or =11 years: < or =21 ng/dL (a.m. peripheral vein specimen)


**Clinical References:**

**Alfalfa (Medicago sativa) IgE**

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.10 Negative
0/1 0.10-0.34 Equivocal/Borderline
1 0.35-0.69 Low Positive
2 0.70-3.49 Moderate Positive
3 3.50-17.49 High Positive
4 17.50-49.99

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Alizarin Red Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This test is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

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**Alkaline Phosphatase, Serum**

**Clinical Information:** Alkaline phosphatase (ALP) is present in a number of tissues including liver, bone, intestine, and placenta. Serum ALP is of interest in the diagnosis of 2 main groups of conditions-hepatobiliary disease and bone disease associated with increased osteoblastic activity. A rise in ALP activity occurs with all forms of cholestasis, particularly with obstructive jaundice. The response of the liver to any form of biliary tree obstruction is to synthesize more ALP. The main site of new enzyme synthesis is the hepatocytes adjacent to the biliary canaliculi. ALP also is elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling, such as Paget's disease, hyperparathyroidism, rickets and osteomalacia, fractures, and malignant tumors. A considerable rise in alkaline phosphatase activity caused by increased osteoblast activity following accelerated bone growth is sometimes seen in children and juveniles.

**Useful For:** Diagnosis and monitoring treatment of liver, bone, intestinal, and parathyroid diseases

**Interpretation:** The elevation in alkaline phosphatase (ALP) tends to be more marked (more than 3 fold) in extrahepatic biliary obstruction (eg, by stone or by cancer of the head of the pancreas) than in intrahepatic obstruction, and is greater the more complete the obstruction. Serum enzyme activities may reach 10 to 12 times the upper limit of normal, returning to normal on surgical removal of the obstruction. The ALP response to cholestatic liver disease is similar to the response of gamma-glutamyltransferase (GGT), but more blunted. If both GGT and ALP are elevated, a liver source of the ALP is likely. Among bone diseases, the highest level of ALP activity is encountered in Paget disease as a result of the action of the osteoblastic cells as they try to rebuild bone that is being resorbed by the uncontrolled activity of osteoclasts. Values from 10 to 25 times the upper limit of the reference interval are not unusual. Only moderate rises are observed in osteomalacia, while levels are generally normal in osteoporosis. In rickets, levels 2 to 4 times normal may be observed. Primary and secondary hyperparathyroidism are associated with slight to moderate elevations of ALP; the existence and degree of elevation reflects the presence and extent of skeletal involvement. Very high enzyme levels are present in patients with osteogenic bone cancer. A considerable rise in ALP is seen in children following accelerated bone growth. In addition, an increase of 2 to 3 times normal may be observed in women in the third trimester of pregnancy, although the interval is very wide and levels may not exceed the upper limit of the reference interval in some cases. The additional enzyme is of placental origin.

**Reference Values:**

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12 years: 185-562 U/L  
13 years: 182-587 U/L  
14 years: 166-571 U/L  
15 years: 138-511 U/L  
16 years: 102-417 U/L  
17 years: 69-311 U/L  
18 years: 52-222 U/L  
> or =19 years: 45-115 U/L  

Females  
4 years: 169-372 U/L  
5 years: 162-355 U/L  
6 years: 169-370 U/L  
7 years: 183-402 U/L  
8 years: 199-440 U/L  
9 years: 212-468 U/L  
10 years: 215-476 U/L  
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16 years: 61-264 U/L  
17-23 years: 52-144 U/L  
24-45 years: 37-98 U/L  
46-50 years: 39-100 U/L  
51-55 years: 41-108 U/L  
56-60 years: 46-118 U/L  
61-65 years: 50-130 U/L  
> or =66 years: 55-142 U/L  

Reference values have not been established for patients that are <4 years of age.


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**ALKI 89503**

**Alkaline Phosphatase, Total and Isoenzymes, Serum**

**Clinical Information:** Alkaline phosphatase (ALP) is present in a number of tissues including liver, bone, intestine, and placenta. The activity of ALP found in serum is a composite of isoenzymes from those sites and, in some circumstances, placental or Regan isoenzymes. Serum ALP is of interest in the diagnosis of 2 main groups of conditions-hepatobiliary disease and bone disease associated with increased osteoblastic activity. A rise in ALP activity occurs with all forms of cholestasis, particularly with obstructive jaundice. The response of the liver to any form of biliary tree obstruction is to synthesize more ALP. The main site of new enzyme synthesis is the hepatocytes adjacent to the biliary canaliculi. ALP also is elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling, such as Paget's disease rickets and osteomalacia, fractures, and malignant tumors. Moderate elevation of ALP may be seen in other disorders such as Hodgkin's disease, congestive heart failure, ulcerative colitis, regional enteritis, and intra-abdominal bacterial infections.

**Useful For:** Diagnosis and treatment of liver, bone, intestinal, and parathyroid diseases Determining the tissue source of increased alkaline phosphatase (ALP) activity in serum Differentiating between liver and bone sources of elevated ALP

**Interpretation:** Total Alkaline Phosphatase (ALP): ALP elevations tend to be more marked (more than 3-fold) in extrahepatic biliary obstructions (eg, by stone or cancer of the head of the pancreas) than in intrahepatic obstructions, and the more complete the obstruction, the greater the elevation. With obstruction, serum ALP activities may reach 10 to 12 times the upper limit of normal, returning to normal upon surgical removal of the obstruction. The ALP response to cholestatic liver disease is similar to the
response of gamma-glutamyltransferase (GGT), but more blunted. If both GGT and ALP are elevated, a liver source of the ALP is likely. Among bone diseases, the highest level of ALP activity is encountered in Paget's disease, as a result of the action of the osteoblastic cells as they try to rebuild bone that is being resorbed by the uncontrolled activity of osteoclasts. Values from 10 to 25 times the upper limit of normal are not unusual. Only moderate rises are observed in osteomalacia, while levels are generally normal in osteoporosis. In rickets, levels 2 to 4 times normal may be observed. Primary and secondary hyperparathyroidism are associated with slight to moderate elevations of ALP; the existence and degree of elevation reflects the presence and extent of skeletal involvement. Very high enzyme levels are present in patients with osteogenic bone cancer. A considerable rise in ALP is seen in children following accelerated bone growth. ALP increases of 2 to 3 times normal may be observed in women in the third trimester of pregnancy, although the reference interval is very wide and levels may not exceed the upper limit of normal in some cases. In pregnancy, the additional enzyme is of placental origin. ALP Isoenzymes: Liver ALP isoenzyme is associated with biliary epithelium and is elevated in cholestatic processes. Various liver diseases (primary or secondary cancer, biliary obstruction) increase the liver isoenzyme. Liver 1 (L1) is increased in some non-malignant diseases (such as cholestasis, cirrhosis, viral hepatitis and in various biliary and hepatic pathologies). It is also increased in malignancies with hepatic metastasis, in cancer of the lungs and digestive tract and in lymphoma. An increase of Liver 2 (L2) may occur in cholestasis and biliary diseases (e.g., cirrhosis, viral hepatitis) and in malignancies (e.g., breast, liver, lung, prostate, digestive tract) with liver metastasis. Osteoblastic bone tumors and hyperactivity of osteoblasts involved in bone remodeling (e.g., Paget's disease) increase the bone isoenzyme. Paget's disease leads to a striking, solitary elevation of bone ALP. The intestinal isoenzyme may be increased in patients with cirrhosis and in individuals who are blood group O or B secretors. The placental (carcinoplacental antigen) and Regan isoenzyme can be elevated in cancer patients.

Reference Values:

ALKALINE PHOSPHATASE

Males
- 4 years: 149-369 U/L
- 5 years: 179-416 U/L
- 6 years: 179-417 U/L
- 7 years: 172-405 U/L
- 8 years: 169-401 U/L
- 9 years: 175-411 U/L
- 10 years: 191-435 U/L
- 11 years: 185-507 U/L
- 12 years: 185-562 U/L
- 13 years: 182-587 U/L
- 14 years: 166-571 U/L
- 15 years: 138-511 U/L
- 16 years: 102-417 U/L
- 17 years: 69-311 U/L
- 18 years: 52-222 U/L
- ≥19 years: 45-115 U/L

Females
- 4 years: 169-372 U/L
- 5 years: 162-355 U/L
- 6 years: 169-370 U/L
- 7 years: 183-402 U/L
- 8 years: 199-440 U/L
- 9 years: 212-468 U/L
- 10 years: 215-476 U/L
- 11 years: 178-526 U/L
- 12 years: 133-485 U/L
- 13 years: 120-449 U/L
- 14 years: 153-362 U/L
- 15 years: 75-274 U/L
- 16 years: 61-264 U/L
- 17-23 years: 52-144 U/L

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
<table>
<thead>
<tr>
<th>Age Group</th>
<th>ALP (IU/L)</th>
<th>ALP (IU/L)</th>
<th>ALP (IU/L)</th>
<th>ALP (IU/L)</th>
<th>ALP (IU/L)</th>
<th>ALP (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-45 years</td>
<td>37-98 U/L</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>46-50 years</td>
<td>39-100 U/L</td>
<td></td>
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<td></td>
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<tr>
<td>51-55 years</td>
<td>41-108 U/L</td>
<td></td>
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<tr>
<td>56-60 years</td>
<td>46-118 U/L</td>
<td></td>
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<tr>
<td>61-65 years</td>
<td>50-130 U/L</td>
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</tr>
<tr>
<td>&gt; or =66 years</td>
<td>55-142 U/L</td>
<td></td>
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</tbody>
</table>

Reference values have not been established for patients who are <4 years of age.

**ALKALINE PHOSPHATASE ISOENZYMES**

**Liver 1%**
- 0-6 years: 5.1-49.0%
- 7-9 years: 3.0-45.0%
- 10-13 years: 2.9-46.3%
- 14-15 years: 7.8-48.9%
- 16-18 years: 14.9-50.5%
- > or =19 years: 27.8-76.3%

**Liver 1**
- 0-6 years: 7.0-112.7 IU/L
- 7-9 years: 7.4-109.1 IU/L
- 10-13 years: 7.8-87.6 IU/L
- 14-15 years: 10.3-75.6 IU/L
- 16-18 years: 13.7-78.5 IU/L
- > or =19 years: 16.2-70.2 IU/L

**Liver 2%**
- 0-6 years: 2.9-13.7%
- 7-9 years: 3.7-12.5%
- 10-13 years: 2.9-22.3%
- 14-15 years: 2.2-19.8%
- 16-18 years: 1.9-12.5%
- > or =19 years: 0.0-8.0%

**Liver 2**
- 0-6 years: 3.0-41.5 IU/L
- 7-9 years: 4.0-35.6 IU/L
- 10-13 years: 3.3-37.8 IU/L
- 14-15 years: 2.2-32.1 IU/L
- 16-18 years: 1.4-19.7 IU/L
- > or =19 years: 0.0-5.8 IU/L

**Bone %**
- 0-6 years: 41.5-82.7%
- 7-9 years: 39.9-85.8%
- 10-13 years: 31.8-91.1%
- 14-15 years: 30.6-85.4%
- 16-18 years: 38.9-72.6%
- > or =19 years: 19.1-67.7%

**Bone**
- 0-6 years: 43.5-208.1 IU/L
- 7-9 years: 41.0-258.3 IU/L
- 10-13 years: 39.4-346.1 IU/L
- 14-15 years: 36.4-320.5 IU/L
- 16-18 years: 32.7-214.6 IU/L
- > or =19 years: 12.1-42.7 IU/L

**Intestine %**
- 0-6 years: 0.0-18.4%
- 7-9 years: 0.0-18.3%
- 10-13 years: 0.0-11.8%
- 14-15 years: 0.0-8.2%
- 16-18 years: 0.0-8.7%
- > or =19 years: 0.0-20.6%
**Intestine**

0-6 years: 0.0-37.7 IU/L  
7-9 years: 0.0-45.6 IU/L  
10-13 years: 0.0-40.0 IU/L  
14-15 years: 0.0-26.4 IU/L  
16-18 years: 0.0-12.7 IU/L  
> or =19 years: 0.0-11.0 IU/L

**Placental**

Not present

**Clinical References:**  

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**FABP2**

**Allergic Bronchopulmonary Aspergillosis Panel II**

**Interpretation:** Total IgE  
Age Related Reference Range  
1-11 months 0-12  
1 year 0-15  
2 year 1-29  
3 year 4-35  
4 year 2-33  
5 year 4-85  
6 year 3-95  
7 year 2-88  
8 year 5-71  
9 year 3-88  
10 year 7-110  
11-14 year 7-111  
15-19 year 6-96  
20-30 year 4-59  
31-50 year 5-79  
51-80 year 3-48

**Aspergillus fumigatus IgE**  
<0.35 kU/L

**Aspergillus fumigatus IgG**  
<46 mcg/mL

**A. fumigatus Mix Gel Diffusion**  
Negative

The gel diffusion method was used to test this patient’s serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms. This test was developed and its performance characteristics determined by Viracor-IBT Laboratories. It has not been cleared or approved by the FDA.
Patients with allergic bronchopulmonary aspergillosis (ABPA) are expected to have the following serological features:

1) A high total IgE of >500 IU/mL, unless patient is receiving corticosteroids.
2) An elevated Aspergillus-specific IgE of class 4 or higher.
3) Positive for Aspergillus-specific IgG.

Allo-isoleucine, Blood Spot

Clinical Information: Maple-syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain-ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). Classic MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple-syrup odor to urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. MSUD is a pan-ethnic condition, but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1:760 live births. The incidence of MSUD is approximately 1:200,000 live births in the general population. Newborn screening includes the measurement of BCAA (Leu, Ile, and Val), which are elevated in MSUD. However, unaffected infants receiving total parenteral nutrition frequently have increased levels of BCAA, a situation that often triggers unnecessary follow-up investigations. Abnormal concentrations of allo-isoleucine (Allo-Ile) are pathognomonic for MSUD. The determination of Allo-Ile (second-tier testing) in the same newborn screening specimens that reveals elevated BCAA allows for positive identification of patients with MSUD and differentiation from BCAA elevations due to dietary artifacts, reducing the occurrence of false-positive newborn screening results. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and Allo-Ile concentrations.

Useful For: Evaluation of newborn screening specimens that test positive for branched-chain amino acids elevations Follow-up of patients with maple-syrup urine disease

Interpretation: Allo-isoleucine is nearly undetectable in individuals not affected by maple-syrup urine disease (MSUD). Accordingly, its presence is diagnostic for MSUD, and its absence is sufficient to rule out MSUD.

Reference Values:
- Allo-isoleucine: <2 nmol/mL
- Leucine: 35-215 nmol/mL
- Isoleucine: 13-130 nmol/mL
- Valine: 51-325 nmol/mL

An interpretive report will also be provided.


Almond Food IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Almond, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Alpha Beta Double-Negative T Cells for Autoimmune Lymphoproliferative Syndrome

Clinical Information: Autoimmune lymphoproliferative syndrome (ALPS) (also known as Canale-Smith syndrome) is a complex clinical disorder of dysregulated lymphocyte homeostasis that is characterized by lymphoproliferative disease, autoimmune cytopenias, splenomegaly, and lymphadenopathy with an increased susceptibility to malignancy. Typically, ALPS is diagnosed by childhood or young adulthood. Genetic defects in the apoptosis (programmed cell death) pathway have been determined for most cases of ALPS. Apoptosis plays a role in normal immune homeostasis by limiting lymphocyte accumulation and autoimmune reactivity. The interaction of the surface receptor CD95 (FAS) and its ligand (CD95L;FASL) triggers the apoptotic pathway in lymphocytes. The following molecular ALPS classification has been established: ALPS Classification Molecular/Genetic Defect in Apoptosis Type Ia CD95 (FAS) mutations(1) Type Ib Heterozygous CD95L (FASLG) mutations(1) Type Ic Homozygous CD95L (FASLG) mutation(2) Type II CASP8 or CASP10 mutations(1,3) Type III Unknown(1,3) Patients with ALPS have an increase in a normally rare population of T cells (typically <1%) that are alpha beta T-cell receptor (TCR)-positive, as well as negative for both CD4 and CD8 coreceptors (double-negative T cells: DNT).(1) The alpha beta TCR+DNT cells from ALPS patients also express an unusual B-cell-specific CD45R isoform, called B220.(4,5) B220 expression on alpha beta TCR+DNT cells has been demonstrated to be a sensitive and specific marker for ALPS and is associated with FAS mutations.(4) Several other diseases can present with an ALPS-like phenotype, including independent conditions like Evans syndrome (a combination of autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura), Rosai-Dorfman disease (massive painless cervical lymphadenopathy that may be accompanied by leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia), and nodular lymphocyte-predominant Hodgkin disease.(1)

Useful For: Diagnosing autoimmune lymphoproliferative syndrome, primarily in patients <45 years of age

Interpretation: The presence of increased circulating T cells (CD3+) that are negative for CD4 and CD8 (double-negative T cells: DNT) and positive for the alpha/beta T-cell receptor (TCR) is required for the diagnosis of autoimmune lymphoproliferative syndrome (ALPS). The laboratory finding of increased alpha beta TCR+DNT cells is consistent with ALPS only with the appropriate clinical picture (nonmalignant lymphadenopathy, splenomegaly, and autoimmune cytopenias). Conversely, there are other immunological disorders, including common variable immunodeficiency (CVID), which have subsets for patients with this clinical picture, but no increase in alpha beta TCR+DNT cells. If the percent of the absolute count of either the alpha beta TCR+DNT cells or alpha beta TCR+DNT B220+ cells is abnormal, additional testing is indicated. All abnormal alpha beta TCR+DNT cell results should be confirmed (for ALPS) with additional testing for defective in vitro lymphocyte apoptosis, followed by confirmatory genetic testing for FAS mutations (contact Mayo Medical Laboratories for test forwarding information).

Reference Values:
Alpha beta TCR+DNT cells
2-18 years: <2% CD3 T cells
19-70+ years: <3% CD3 T cells
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT cells
2-18 years: <35 cells/mcL
19-70+ years: <35 cells/mcL
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <0.4% CD3 T cells
19-70+ years: <0.3% CD3 T cells
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <7 cells/mcL

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19-70+ years: <6 cells/mcL
Reference values have not been established for patients that are less than 24 months of age.


**FALG**

**Alpha Lactalbumin IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FA1GP**

**Alpha-1-Acid Glycoprotein**

**Reference Values:**
Adults: 39 â€“ 115 mg/dL

**CA1A**

**Alpha-1-Antitrypsin Clearance, Feces and Serum**

**Clinical Information:** Alpha-1-antitrypsin (A1A) is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. A1A clearance is reliable for measuring protein loss distal to the pylorus. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow’s milk.

**Useful For:** Diagnosing protein-losing enteropathies

**Interpretation:** Elevated alpha-1-antitrypsin (A1A) clearance suggests excessive gastrointestinal protein loss. (The positive predictive value of the test has been found to be 97.7% and the negative predictive value is 75%.) Patients with protein-losing enteropathies generally have A1A clearance values >50 mL/24 hours and A1A stool concentrations >100 mg/mL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

**Reference Values:**
Clearance: < or =27 mL/24 hours
Fecal alpha-1-antitrypsin concentration: < or =54 mg/dL
Serum alpha-1-antitrypsin concentration: 100-190 mg/dL
**Clinical References:**

### A1APP 26953

**Alpha-1-Antitrypsin Phenotype**

**Clinical Information:** Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. Most normal individuals have the M phenotype (M, M1, or M2). Over 99% of M phenotypes are genetically MM. In the absence of family studies, the phenotype (M) and quantitative level can be used to infer the genotype (MM). The most common alleles associated with a quantitative deficiency are Z and S. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

**Useful For:** Identification of homozygous and heterozygous phenotypes of the alpha-1-antitrypsin deficiency

**Interpretation:** There are >40 alpha-1-antitrypsin (A1A) phenotypes (most of these are associated with normal quantitative levels of protein). The most common normal phenotype is M (M, M1, or M2), and >90% of Caucasians are genetically homozygous M (MM). A1A deficiency is usually associated with the Z phenotype (homozygous ZZ), but SS and SZ are also associated with decreased A1A levels.

**Reference Values:**

**ALPHA-1-ANTITRYPSIN**

100-190 mg/dL

**ALPHA-1-ANTITRYPSIN PHENOTYPE**

The interpretive report will identify the alleles present. For rare alleles, the report will indicate whether or not they have been associated with reduced quantitative levels of alpha-1-antitrypsin.

**Clinical References:**

### A1ALC 61767

**Alpha-1-Antitrypsin Proteotype S/Z by LC-MS/MS, Serum**

**Clinical Information:** Alpha-1-antitrypsin (A1A) is a protein that inhibits the enzyme neutrophil elastase. It is predominantly synthesized in the liver and secreted into the bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema, which initially affects the lung bases (as opposed to smoking-related emphysema, which presents with upper-lung field emphysema). Patients may become symptomatic in their 30s and 40s. The most frequent symptoms reported in a National Institute of Health study of 1,129 patients with severe deficiency (mean age 46 years) included cough (42%), wheezing (65%), and dyspnea with exertion (84%). Many patients were misdiagnosed as having asthma. It is estimated that approximately one-sixth of all lung transplants are for A1A deficiency. Liver disease can also occur, particularly in children; it occurs much less commonly than emphysema in adults. A1A deficiency is a relatively common disorder in Northern European Caucasians. The diagnosis of A1A deficiency is initially made by quantitation of protein levels in serum followed by determination of specific allelic variants by isoelectric focusing (IEF). While there are many different alleles in this gene, only 3 are common. The 3 major alleles include: M (full functioning, normal allele), S (associated with reduced levels of protein), and Z (disease-causing mutation associated with liver disease and premature emphysema). The S and Z alleles account for the
majority of the abnormal alleles detected in affected patients. As a codominant disorder, both alleles are expressed. An individual of SZ or S-null genotype may have a small increased risk for emphysema (but not liver disease) due to slightly reduced protein levels. On the other hand, an individual with the ZZ genotype is at greater risk for early onset liver disease and premature emphysema. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. Historically, IEF has been the primary method for characterizing variants, though in some cases the interpretation is difficult and prone to error. Serum quantitation is helpful in establishing a diagnosis, but can be influenced by other factors. A proteomic method using trypsin-digested sera can detect the mutated peptides of the S and Z alleles, but can miss disease alleles other than the S and Z alleles. This test combines all of these methods to provide a comprehensive result.

**Useful For:** Determining the specific proteotype for prognosis and genetic counseling for patients with alpha-1-antitrypsin deficiency

**Interpretation:** For each of the possible alpha-1-antitrypsin (A1A) genotypes there is an expected range for the total serum level of A1A. However, a number of factors can influence either the A1A serum level or the A1A proteotype results, including acute illness (A1A is an acute-phase reactant), protein replacement therapy, the presence of other rare variants, or the presence of DNA polymorphisms. When the serum level differs from what is expected for that proteotype (ie, discordant), additional studies are performed to ensure the most appropriate interpretation of test results. Additional follow-up may include A1A phenotyping by isoelectric focusing, obtaining additional clinical information, and DNA sequencing. See Alpha-1-Antitrypsin Reflex Table in Special Instructions.

**Reference Values:**

**ALPHA-1-ANTITRYPSIN**

100-190 mg/dL

**ALPHA-1-ANTITRYPSIN PROTEOTYPE**

Negative for S and Z phenotype (Non S Non Z)


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**Alpha-1-Antitrypsin, Random, Feces**

**Clinical Information:** Alpha-1-antitrypsin (A1A) is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. A1A clearance is reliable for measuring protein loss distal to the pylorus. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple's intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow's milk.

**Useful For:** Diagnosing protein-losing enteropathies, especially when used in conjunction with serum alpha-1-antitrypsin (A1A) levels as a part of A1A clearance studies (see CA1A / Alpha-1-Antitrypsin Clearance, Feces and Serum; preferred test)

**Interpretation:** Patients with protein-losing enteropathies generally have alpha-1-antitrypsin stool concentrations >100 mg/mL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

**Reference Values:**

< or =54 mg/dL

Alpha-1-Antitrypsin, Serum

Clinical Information: Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

Useful For: Workup of individuals with suspected disorders such as familial chronic obstructive lung disease Diagnosis of alpha-1-antitrypsin deficiency

Interpretation: Patients with serum levels <70 mg/dL may have a homozygous deficiency and are at risk for early lung disease. Alpha-1-antitrypsin proteotyping should be done to confirm the presence of homozygous deficiency alleles. If clinically indicated, patients with serum levels <125 mg/dL should be proteotyped in order to identify heterozygous individuals. Heterozygotes do not appear to be at increased risk for early emphysema.

Reference Values: 100-190 mg/dL


Alpha-1-Microglobulin, 24 Hour, Urine

Clinical Information: Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily. It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

Useful For: Assessment of renal tubular injury or dysfunction Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

Interpretation: Alpha-1-microglobulin above the reference values may be indicative of a proximal tubular dysfunction.

Reference Values: > or =16 years: <19 mg/24 hours
RA1M
84448
Alpha-1-Microglobulin, Random, Urine
Clinical Information: Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocarlin protein superfamily. (1) It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized. (1) Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated urinary alpha-1-microglobulin excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that 1 test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

Useful For: Assessment of renal tubular injury or dysfunction Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

Interpretation: Alpha-1-microglobulin above the reference values may indicate a proximal tubular dysfunction. As suggested in the literature, 7 mg/g creatinine is an upper reference limit for pediatric patients of 1 month to 15 years of age.

Reference Values:
<50 years: <13 mg/g creatinine
> or =50 years: <20 mg/g creatinine


APSM
9084
Alpha-2 Plasmin Inhibitor, Plasma
Clinical Information: Alpha-2 plasmin inhibitor (antiplasmin) is synthesized in the liver with a biological half-life of approximately 3 days. It inactivates plasmin, the primary fibrinolytic enzyme responsible for remodeling the fibrin thrombus, and binds fibrin, together with factor XIIIa, making the clot more difficult to lyse. Absence of alpha-2 plasmin inhibitor results in uncontrolled plasmin-mediated
breakdown of the fibrin clot and is associated with increased risk of bleeding.

**Useful For:** Diagnosing congenital alpha-2 plasmin inhibitor deficiencies (rare) Providing a more complete assessment of disseminated intravascular coagulation, intravascular coagulation and fibrinolysis, or hyperfibrinolysis (primary fibrinolysis), when measured in conjunction with fibrinogen, fibrin D-dimer, fibrin degradation products, soluble fibrin monomer complex, and plasminogen Evaluating liver disease Evaluating the effects of fibrinolytic or antifibrinolytic therapy

**Interpretation:** Patients with congenital homozygous deficiency (with levels of <10%) are clinically affected (bleeding). Heterozygotes having levels of 30% to 60% of mean normal activity are usually asymptomatic. Lower than normal levels may be suggestive of consumption due to activation of plasminogen and its inhibition by alpha-2 plasmin inhibitor. The clinical significance of high levels of alpha-2 plasmin inhibitor is unknown.

**Reference Values:**
Adults: 80-140%
Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =50%) which reach adult levels within 5 to 7 days postnatal.*
Healthy, premature infants (30-36 weeks gestation) may have mildly decreased levels which reach adult levels in < or =90 days postnatal.*
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**

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**Alpha-2-Macroglobulin, Serum**

**Clinical Information:** Alpha-2-macroglobulin is a protease inhibitor and is 1 of the largest plasma proteins. It transports hormones and enzymes, exhibits effector and inhibitor functions in the development of the lymphatic system, and inhibits components of the complement system and hemostasis system. Increased levels of alpha-2-macroglobulin are found in nephrotic syndrome when other lower molecular weight proteins are lost and alpha-2-macroglobulin is retained because of its large size. In patients with liver cirrhosis and diabetes, the levels are found to be elevated. Patients with acute pancreatitis exhibit low serum concentrations which correlate with the severity of the disease. In hyperfibrinolytic states, after major surgery, in septicemia and severe hepatic insufficiency, the measured levels of alpha-2-macroglobulin are often low. Acute myocardial infarction patients with low alpha-2-macroglobulin have been reported to have a significantly better prognosis with regard to the >1 year survival time.

**Useful For:** Evaluation of patients with nephrotic syndrome and pancreatitis

**Interpretation:** Values are elevated in the nephrotic syndrome in proportion to the severity of protein loss (lower molecular weight). Values are low in proteolytic diseases such as pancreatitis.

**Reference Values:**
100-280 mg/dL

**Clinical References:**
**Alpha-Amylase, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Alpha-Fetoprotein (AFP) L3% and Total, Hepatocellular Carcinoma Tumor Marker, Serum**

**Clinical Information:** Worldwide, hepatocellular carcinoma is the third leading cause of death from cancer. (1) While hepatocellular carcinoma can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of suspected hepatocellular carcinoma. However, increased serum concentrations of AFP might be found in chronic hepatitis and liver cirrhosis, as well as in other tumor types (eg, germ cell tumors[2]), decreasing the specificity of AFP testing for hepatocellular carcinoma. Furthermore,AFP is not expressed at high levels in all hepatocellular carcinoma patients, resulting in decreased sensitivity, especially in potentially
curable small tumors. AFP is differentially glycosylated in several hepatic diseases. For example, UDP-alpha-1→6-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation.(3) This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following electrophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP that is most closely associated with hepatocellular carcinoma is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP < or =200 ng/mL, which may result from a variety of benign pathologies, such as chronic liver diseases. AFP-L3 should be utilized as an adjunct to high-resolution ultrasound for surveillance of individuals at significant risk for developing hepatic lesions, as described below.

**Useful For:** Distinguishing between hepatocellular carcinoma and chronic liver disease Monitoring individuals with hepatic cirrhosis from any etiology for progression to hepatocellular carcinoma Surveillance for development of hepatocellular carcinoma in individuals with a positive family history of hepatic cancer Surveillance for development of hepatocellular carcinoma in individuals within specific ethnic and gender groups who do not have hepatic cirrhosis, but have a confirmed diagnosis of chronic infection by hepatitis B acquired early in life including: - African males above the age of 20 - Asian males above the age of 40 - Asian females above the age of 50

**Interpretation:** Alpha-fetoprotein (AFP)-L3 > or =10% is associated with a 7-fold increased risk of developing hepatocellular carcinoma. Patients with AFP-L3 > or =10% should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. Total serum AFP >200 ng/mL is highly suggestive of a diagnosis of hepatocellular carcinoma. In patients with liver disease, a total serum AFP of >200 ng/mL is near 100% predictive of hepatocellular carcinoma. With decreasing total AFP levels, there is an increased likelihood that chronic liver disease, rather than hepatocellular carcinoma, is responsible for the AFP elevation. Based on a retrospective study at the Mayo Clinic, for patients with total AFP levels < or =200 ng/mL, AFP-L3 specificity approaches 100% for hepatocellular carcinoma when its percentage exceeds 35% of the total AFP.(4) AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life.

**Reference Values:**
- <10%

**Clinical References:**
5. Package insert: LBA AFP-L3, Wako Diagnostics, Richmond, VA. 06.1.24K02

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**Alpha-Fetoprotein (AFP) Tumor Marker, Serum**

**Clinical Information:** Alpha-fetoprotein (AFP) is a glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including hepatocellular carcinoma, hepatoblastoma, and nonseminomatous germ cell tumors of the ovary and testis (eg, yolk sac and embryonal carcinoma). Most studies report elevated AFP concentrations in approximately 70% of patients with hepatocellular carcinoma. Elevated AFP concentrations are found in 50% to 70% of patients with nonseminomatous testicular tumors. AFP is elevated during pregnancy. Persistence of AFP in the mother following birth is a rare hereditary condition. Neonates have markedly elevated AFP levels (>100,000 ng/mL) that rapidly fall to below 100 ng/mL by 150 days and gradually return to normal over their first year. Concentrations of AFP above the reference range also have been found in serum of patients with benign liver disease (eg, viral hepatitis, cirrhosis), gastrointestinal tract tumors and, along with carcinoembryonic antigen in ataxia telangiectasia. The biological half-life of AFP is approximately 5 days.
Useful For: The follow-up management of patients undergoing cancer therapy, especially for testicular and ovarian tumors and for hepatocellular carcinoma. Often used in conjunction with human chorionic gonadotropin (2).

Interpretation: Alpha-fetoprotein (AFP) levels may be elevated in association with a variety of malignancies or benign diseases. Failure of the AFP value to return to normal by approximately 1 month after surgery suggests the presence of residual tumor. Elevation of AFP after remission suggests tumor recurrence; however, tumors originally producing AFP may recur without an increase in AFP.

Reference Values:
<6.0 ng/mL
Reference values are for nonpregnant subjects only; fetal production of AFP elevates values in pregnant women.
Range for newborns is not available, but concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 months of life. (See literature reference: Ped Res 1981;15:50-52) For further interpretive information, see Alpha-Fetoprotein (AFP) in Special Instructions.
Serum markers are not specific for malignancy, and values may vary by method.


Alpha-Fetoprotein (AFP), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Alpha-fetoprotein (AFP) measurement in serum is used in the management of patients with hepatocellular carcinoma (HCC). Measurement of AFP in ascites fluid might be useful, when used in conjunction with cytology, in patients with a history of HCC and in whom a cause of peritoneal fluid accumulation is uncertain.

Useful For: An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation.

Interpretation: A peritoneal fluid alpha-fetoprotein (AFP) concentration >6.0 ng/mL is suspicious but not diagnostic of ascites related to hepatocellular carcinoma (HCC). This clinical decision limit cutoff yielded a sensitivity of 58%, specificity of 96% in a study of 137 patients presenting with ascites. AFP concentrations were significantly higher in ascites caused by HCC. Ascites caused by malignancies other than HCC routinely had AFP concentrations <6.0 ng/mL. Therefore, negative results should be interpreted with caution.

Reference Values:
An interpretive report will be provided.

Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum

Clinical Information: Analytes: Alpha-fetoprotein (AFP) is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from the nonpregnancy level of 0.20 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect (NTD), AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation; thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal distress situations such as threatened abortion and fetal demise also may show AFP elevations. Increased maternal serum AFP values also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP values have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18. Risks for these syndrome disorders are only provided with the use of multiple marker screening (QUAD / Quad Screen [Second Trimester] Maternal, Serum). Measurement of maternal serum AFP values is a standard tool used in obstetrical care to identify pregnancies that may have an increased risk for NTD. The screen is performed by measuring AFP in maternal serum and comparing this value to the median AFP value in an unaffected population to obtain a multiple of the median (MoM). The laboratory has established a MoM cutoff of 2.50 MoM, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered.

Useful For: Prenatal screening for open neural tube defect

Interpretation: Neural tube defects (NTD): A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of NTDs. A screen-positive result indicates that the calculated AFP MoM is > or =2.50 MoM and may indicate an increased risk for open NTDs. The actual risk depends on the level of AFP and the individual's pre-test risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD, but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with an open NTD have elevated AFP MoM values >2.5. Follow up: Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (ie, weight, diabetic status, gestational dating, etc.). If any information is incorrect the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD screen-positive results. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTDs) are typically offered.

Reference Values:
NEURAL TUBE DEFECTS
An AFP multiple of the median (MoM) <2.5 is reported as screen negative. AFP MoMs > or =2.5 (singleton and twin pregnancies) are reported as screen positive.

An interpretive report will be provided.

Alpha-Fetoprotein (AFP), Spinal Fluid

Clinical Information: Alpha-fetoprotein (AFP) is an oncofetal glycoprotein, homologous with albumin that is produced both in early fetal life and in tumors arising from midline embryonic structures. AFP is synthesized in the yolk sac, liver, and gastrointestinal tract of the fetus. In adults, the liver synthesizes AFP. AFP is not normally expressed in the central nervous system (CNS). AFP levels in liver are increased in hepatomas and hematocellular and colon carcinomas, as well as in germ-cell tumors arising from the ovaries and nonseminomatous germ-cell tumors of the testes, testicular teratocarcinomas, and primary germ-cell tumors arising within the CNS. The presence of germinomas in the CNS and CNS involvement in metastatic cancer and meningeal carcinomatosis results in increased levels of AFP in cerebrospinal fluid.

Useful For: An adjunct in the diagnosis of central nervous system (CNS) germinomas and meningeal carcinomatosis Evaluating germ-cell tumors, including testicular cancer metastatic to the CNS in conjunction with beta-human chorionic gonadotropin measurement(1) An adjunct in distinguishing between suprasellar dysgerminomas and craniopharyngiomas A supplement to cerebrospinal fluid cytologic analysis

Interpretation: Alpha-fetoprotein (AFP) concentrations that exceed the upper end of normal are consistent with the presence of central nervous system germinoma, meningeal carcinomatosis, or metastatic nonseminomatous testicular cancer. AFP is not elevated in the presence of a craniopharyngioma.

Reference Values:
<1.5 ng/mL
Values for alpha-fetoprotein in cerebrospinal fluid have not been formally established for newborns and infants. The available literature indicates that by 2 months of age, levels comparable to adults should be reached.(Ann Clin Biochem 2005;42:24-29)


Alpha-Fetoprotein, Amniotic Fluid

Clinical Information: Alpha-fetoprotein (AFP) is a single polypeptide chain glycoprotein with a molecular weight of approximately 70,000 daltons. Synthesis of AFP occurs primarily in the liver and yolk sac of the fetus. It is secreted in fetal serum, reaching a peak at approximately 13 weeks gestation, after which it rapidly declines until about 22 weeks gestation and then gradually declines until term. Transfer of AFP into maternal circulation is accomplished primarily through diffusion across the placenta. Maternal serum AFP levels rise from the normal nonpregnancy level of 0.20 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Other fetal abnormalities such as omphalocele, gastrochisis, congenital renal disease, and esophageal atresia; and other fetal distress situations such as threatened abortion, prematurity, and fetal demise, may also show AFP elevations. Decreased amniotic fluid AFP values may be seen when gestational age has been overestimated.

Useful For: Screening for open neural tube defects or other fetal abnormalities Follow-up testing for patients with elevated serum alpha-fetoprotein results or in conjunction with cytogenetic testing

Interpretation: A diagnostic alpha-fetoprotein (AFP) cutoff level of 2.0 multiples of median (MoM),
followed by acetylcholinesterase (AChE) confirmatory testing on positive results, is capable of detecting 96% of open spina bifida cases with a false-positive rate of only 0.06% in non blood-stained specimens. AChE analysis is an essential confirmatory test for all amniotic fluid specimens with positive AFP results. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of open communication between fetal central nervous system (eg, open neural tube defects), or to a lesser degree, fetal circulation. All amniotic fluid specimens testing positive for AFP will have the AChE test performed. False-positive AChE may occur from a bloody tap, which may cause both elevated AFP and AChE levels.

Reference Values:
< or =2.0 multiples of median (MoM)


FUCT

Alpha-Fucosidase, Fibroblasts

Clinical Information: Fucosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent alpha-L-fucosidase enzyme activity. This enzyme is involved in degrading asparagine-linked, fucose-containing complex molecules (oligosaccharides, glycoasparagines) present in cells. Reduced or absent activity of this enzyme results in the abnormal accumulation of these undigested molecules in the tissues and body fluids. Although the disorder is pan ethnic, the majority of reported patients with fucosidosis have been from Italy and the southwestern United States. Severe and mild subgroups of fucosidosis, designated types I and II, have been described, although recent data suggests individual patients may represent a continuum within a wide spectrum of severity. The more severe type is characterized by infantile onset, rapid psychomotor regression, and severe neurologic deterioration. Additionally, dysostosis multiplex and elevated sweat sodium chloride are frequent findings. Death typically occurs within the first decade of life. Those with the milder phenotype express comparatively mild psychomotor and neurologic regression, radiologic signs of dysostosis multiplex, and skin lesions (angiokeratoma corporis diffusum). Normal sweat salinity, the presence of the skin lesions, and survival into adulthood most readily distinguish milder from more severe phenotypes. An initial diagnostic workup includes a multienzyme screening assay for several oligosaccharidoses, including fucosidosis, in leukocytes or fibroblasts (OLIWB / Oligosaccharidoses Screen, Leukocytes or OLITC / Oligosaccharidoses Screen, Fibroblasts). If the screening assay is suggestive of fucosidosis, enzyme analysis of alpha-L-fucosidase can confirm the diagnosis. Enzyme analysis should be pursued in cases with strong clinical suspicion regardless of the screening result. Sequencing of FUCA1 allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members.

Useful For: Diagnosis of fucosidosis

Interpretation: Low alpha-fucosidase suggests fucosidosis when accompanied with clinical findings. Some patients exhibit measurable activity minimally below the normal range. These patients are not likely to have fucosidosis.

Reference Values:
> or =0.41 nmol/min/mg protein

Alpha-Fucosidase, Leukocytes

Clinical Information: Fucosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent alpha-L-fucosidase enzyme activity. This enzyme is involved in degrading asparagine-linked, fucose-containing complex molecules (oligosaccharides, glycoasparagines) present in cells. Reduced or absent activity of this enzyme results in the abnormal accumulation of these undigested molecules in the tissues and body fluids. Severe and mild subgroups of fucosidosis, designated types I and II, have been described, although recent data suggests individual patients may represent a continuum within a wide spectrum of severity. The more severe type is characterized by infantile onset, rapid psychomotor regression, and severe neurologic deterioration. Additionally, dysostosis multiplex and elevated sweat sodium chloride are frequent findings. Death typically occurs within the first decade of life. Those with the milder phenotype express comparatively mild psychomotor and neurologic regression, radiologic signs of dysostosis multiplex and skin lesions (angiokeratoma corporis diffusum). Normal sweat salinity, the presence of the skin lesions, and survival into adulthood most readily distinguish milder from more severe phenotypes. Although the disorder is panethnic, the majority of reported patients with fucosidosis have been from Italy and southwestern United States. To date, about 100 cases have been reported worldwide. An initial diagnostic workup includes a multienzyme screening assay for several oligosaccharidoses, including fucosidosis, in leukocytes or fibroblasts (OLIWB / Oligosaccharidoses Screen, Leukocytes or OLITC / Oligosaccharidoses Screen, Fibroblasts). If the screening assay is suggestive of fucosidosis, enzyme analysis of alpha-L-fucosidase can confirm the diagnosis.

Useful For: Detection of fucosidosis

Interpretation: Values <0.32 nmol/min/mg protein are consistent with a diagnosis of fucosidosis.

Reference Values:
> or =0.32 nmol/min/mg protein


Alpha-Gal Panel

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 > or = 100 Very High Positive

Reference Values:

**Beef IgE**<0.35 kU/L
**Lamb/Mutton IgE**<0.35 kU/L
**Pork IgE**<0.35 kU/L
**Galactose-alpha-1,3-galactose (Alph Gal) IgE**<0.35 kU/L

Previous reports (JACI 2009; 123:426-433) have demonstrated that patients with IgE antibodies to...
galactose-α-1, 3-galactose are at risk for delayed anaphylaxis, angioedema, or urticaria following consumption of beef, pork, or lamb.

* This test was developed and its performance characteristics determined by Viracor-IBT Laboratories. It has not been cleared or approved by the FDA.

AGABS89407

**Alpha-Galactosidase, Blood Spot**

**Clinical Information:** Fabry disease is an X-linked recessive lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (a-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body, in particular, the kidney, heart, and brain. More than 150 mutations in the GLA gene have been identified in individuals diagnosed with Fabry disease. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in males with <1% a-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (pain crises in the extremities), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. In addition, progressive renal involvement leading to end-stage renal disease typically occurs in adulthood followed by cardiovascular and cerebrovascular disease. The estimated incidence is 1 in 40,000 males. Males with residual a-Gal A activity may present with either of 2 variant forms of Fabry disease (renal or cardiac) with onset of symptoms later in life. Individuals with the renal variant typically present in the third decade with the development of renal insufficiency and, ultimately, end-stage renal disease. These individuals may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy, mitral insufficiency, or conduction abnormalities in the fourth decade. The cardiac variant is not associated with renal failure. Variant forms of Fabry disease may be underdiagnosed. Enzyme replacement therapy became available for Fabry disease treatment in the early 2000s, which lead to significant clinical improvement unless irreversible damage had already occurred. For this reason, early detection of Fabry disease through newborn screening is expected to improve the outcome of affected patients and has recently been implemented in 2 US states. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected and may have a-Gal A activity in the normal range; therefore, additional studies including molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) are recommended to detect carriers. Reduced or absent a-Gal A in blood spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing mutation in affected patients and carrier detection in females. See Fabry Disease Testing Algorithm in Special Instructions.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of Fabry disease Follow-up to an abnormal newborn screen for Fabry disease

**Interpretation:** In male patients, results <1.2 nmol/mL/hour in properly submitted specimens are consistent with Fabry disease. Normal results (> or =1.2 nmol/mL/hour) are not consistent with Fabry disease. In female patients, normal results (> or =2.8 nmol/mL/hour) in properly submitted specimens are typically not consistent with carrier status for Fabry disease; however, enzyme analysis, in general, is not sufficiently sensitive to detect all carriers. Because a carrier range has not been established in females, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) should be considered when alpha-galactosidase A activity is <2.9 nmol/mL/hour, or if clinically indicated. Pseudodeficiency results in low measured alpha-galactosidase A, but is not consistent with Fabry disease. See Fabry Disease Testing Algorithm in Special Instructions.

**Reference Values:**

- Males: > or =1.2 nmol/mL/h
- Females: > or =2.8 nmol/mL/h

An interpretive report will be provided.

**Clinical References:**
2. De Schoenmakere G, Poppe B,
Alpha-Galactosidase, Serum

**Clinical Information:** Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body; in particular, the kidney, heart, and brain. Fabry disease is caused by mutations within the GLA gene, and more than 630 mutations have been identified in individuals diagnosed with Fabry disease. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in males with <1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to end-stage renal disease typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3,000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Males with residual alpha-Gal A activity may present with either a renal or cardiac variant form of Fabry disease with onset of symptoms later in life. Individuals with the renal variant typically present in the third decade with the development of renal insufficiency and, ultimately, end-stage renal disease. These individuals may or may not exhibit other symptoms of the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy, mitral insufficiency, or conduction abnormalities in the fourth decade. Variant forms of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and yet they may have alpha-Gal A activity in the normal range. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) is recommended to detect carriers. Absent or reduced alpha-Gal A in blood spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing mutation in males and females. See Fabry Disease Testing Algorithm in Special Instructions.

**Useful For:** Diagnosis of Fabry disease in males Serum testing is the preferred screen for Fabry disease

**Interpretation:** Deficiency (<0.016 U/L) of alpha-galactosidase in properly submitted specimens is diagnostic for Fabry disease in males. If concerned about specimen integrity, please recheck using leukocyte testing (AGA / Alpha-Galactosidase, Leukocytes). Urine sediment analysis (CTSA / Ceramide Trihexosides and Sulfatides, Urine) for the accumulating trihexoside substrate is also recommended. Carrier females usually have alpha-galactosidase levels in the normal range; therefore, molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) is recommended as the appropriate diagnostic test for females.

**Reference Values:**
0.074-0.457 U/L

Note: Results from this assay are not useful for carrier determination. Carriers usually have levels in the normal range.

**Clinical References:**
Alpha-Globin Gene Analysis

Reference Values:
Only orderable as part of a profile. For more information see ATHAL / Alpha-Globin Gene Analysis.

Clinical Information: The thalassemias are a group of inherited conditions characterized by decreased synthesis of one or more of the globin chains, resulting in an imbalance in the relative amounts of the alpha and beta chains. The excess normal chains precipitate in the cell, damaging the membrane and leading to premature red blood cell destruction. Additionally, the defect in hemoglobin synthesis produces a hypochromic, microcytic anemia. The frequency of thalassemia is due to the protective advantage against malaria that it gives carriers. Consequently, thalassemias are prevalent in populations from equatorial regions in the world where malaria is endemic. Alpha-thalassemia is caused by decreased synthesis of alpha-globin chains. Four alpha-globin genes are normally present (2 on each chromosome 16). One, 2, 3, or 4 alpha-globin genes may be deleted or, less commonly, contain mutations. Deletions account for approximately 90% of disease-causing alleles in alpha thalassemia. Phenotypically, these deletions result in 4 categories of disease expression: -Deletion of 1 alpha-chain: Silent carrier state, with a normal phenotype -Deletion of 2 alpha-chains: Alpha-thalassemia trait (alpha-1 thalassemia), with mild hematologic changes but no major clinical difficulties -Deletion of 3 alpha-chains: Hemoglobin H disease, which is extremely variable but usually includes anemia due to hemolysis, jaundice, and hepatosplenomegaly -Deletion of all 4 alpha-chains: Hemoglobin Bart, with hydrops fetalis and almost invariably in utero demise Less frequently, alpha-thalassemia results from single point mutations. The most common nondeletion mutation is hemoglobin Constant Spring (HbCS) (HBA2: c.427T >C). Point mutations other than HbCS and alpha-thalassemia Saudi are not detected by this assay. Alpha-thalassemia occurs in all ethnic groups but is especially common individuals of Southeast Asian and African ancestry. It is also frequent in individuals of Mediterranean ancestry. The carrier frequency is estimated to be 1 in 20 for Southeast Asians, 1 in 30 for African Americans, and 1 in 30 to 1 in 50 for individuals of Mediterranean ancestry. Both deletional and nondeletional (caused by point mutations) forms of alpha-thalassemia are found in individuals with Mediterranean ancestry. Deletions in cis (deletions on the same chromosome) are rare in African or Mediterranean populations, but are prevalent in Asian populations. Couples in which both partners carry deletions in cis are at risk of having a child with the fatal hemoglobin Bart hydrops fetalis syndrome.

Useful For: Diagnosis of alpha-thalassemia Prenatal diagnosis of deletional alpha-thalassemia Carrier screening for individuals from high-risk populations for alpha-thalassemia

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

**AGLYP**

**Alpha-Glycerophosphate Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**IDSWB**

**Alpha-L-Iduronidase, Blood**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAG). Accumulation of GAG (previously called mucopolysaccharides; MPS) in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG. MPS disorders involve multiple organ systems characterized by coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. More than 100 mutations have been reported in individuals with MPS I. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS I typically demonstrates elevated levels of urinary GAGs with increased amounts of both dermatan and heparan sulfate being detected (MPSSC / Mucopolysaccharides [MPS] Screen, Urine). Reduced or absent activity of alpha L-iduronidase can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in relatives. To date, a clear genotype-phenotype correlation has not been established.

**Useful For:** Diagnosis of mucopolysaccharidosis I, Hurler, Scheie, and Hurler-Scheie syndromes

**Interpretation:** Specimens with results <1.0 nmol/h/mL in properly submitted specimens are consistent with alpha-L-iduronidase deficiency (mucopolysaccharidosis I). Further differentiation between Hurler, Scheie, and Hurler-Scheie is dependent upon the clinical findings. Normal results (≥ or =1.0 nmol/h/mL) are not consistent with alpha-L-iduronidase deficiency.

**Reference Values:**
> or ≥1.0 nmol/h/mL

An interpretive report will be provided.

Alpha-L-Iduronidase, Blood Spot

**Clinical Information:** The mucopolysaccharidoses are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAG). Accumulation of GAG (previously called mucopolysaccharides; MPS) in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG. MPS disorders involve multiple organ systems characterized by coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. More than 100 mutations have been reported in individuals with MPS I. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS I typically demonstrates elevated levels of urinary GAG (MPSQN / Mucopolysaccharides [MPS], Quantitative, Urine) and increased amounts of both dermatan and heparan sulfate detected on thin-layer chromatography (MPSSC / Mucopolysaccharides [MPS] Screen, Urine). Reduced or absent activity of alpha-L-iduronidase in blood spots, fibroblasts (IDST / Alpha-L-Iduronidase, Fibroblasts), leukocytes, or whole blood (IDSWB / Alpha-L-Iduronidase, Blood) can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in relatives. To date, a clear genotype-phenotype correlation has not been established.

**Useful For:** Diagnosis of mucopolysaccharidosis I, Hurler, Scheie, and Hurler-Scheie syndromes using dried blood spot specimens

**Interpretation:** Specimens with results <1.0 nmol/hour/mL in properly submitted specimens are consistent with alpha-L-iduronidase deficiency (mucopolysaccharidosis I). Further differentiation between Hurler, Scheie, and Hurler-Scheie is dependent on the clinical findings. Normal results (≥1.0 nmol/hour/mL) are not consistent with alpha-L-iduronidase deficiency.

**Reference Values:**

> or =1.0 nmol/h/mL

An interpretive report will be provided.

**Clinical References:**

**Alpha-L-Iduronidase, Fibroblasts**

**Clinical Information:** The mucopolysaccharidoses are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAG). Accumulation of GAG (previously called mucopolysaccharides; MPS) in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG. MPS disorders involve multiple organ systems characterized by coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. More than 100 mutations have been reported in individuals with MPS I. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS I typically demonstrates elevated levels of urinary GAG (MPSQN / Mucopolysaccharides [MPS], Quantitative, Urine) and increased amounts of both dermatan and heparan sulfate detected on thin-layer chromatography (MPSSC / Mucopolysaccharides [MPS] Screen, Urine). Reduced or absent activity of alpha-L-iduronidase in blood spots, fibroblasts (IDST / Alpha-L-Iduronidase, Fibroblasts), leukocytes, or whole blood (IDSWB / Alpha-L-Iduronidase, Blood) can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in relatives. To date, a clear genotype-phenotype correlation has not been established.

**Useful For:** Diagnosis of mucopolysaccharidosis I (MPS I), Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S) in fibroblasts

**Interpretation:** Mucopolysaccharidosis I is characterized by very low or absent activity of alpha-L-iduronidase; differentiation between Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S) is based on clinical findings.

**Reference Values:**
> or ≥ 0.87 nmol/min/mg protein

**Clinical References:**
immune response to allergens that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders

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### Alpha-Mannosidase, Fibroblasts

**Clinical Information:** Alpha-mannosidosis is an autosomal recessive lysosomal storage disorder
caused by reduced or absent acid alpha-mannosidase enzyme activity. This enzyme is involved in
glycoprotein catabolism, with absent or reduced activity resulting in the accumulation of undigested
mannose-containing complex oligosaccharides in the lysosomes, disrupting the normal functioning of
cells. Clinical features and severity of symptoms are widely variable within alpha-mannosidosis, but in
general, the disorder is characterized by skeletal abnormalities, immune deficiency, hearing impairment,
and mental retardation. Three clinical subtypes of the disorder have been described and they vary with
respect to age of onset and clinical presentation. Type 1 is generally classified by a mild presentation and
slow progression with onset after 10 years of age and absence of skeletal abnormalities. Type 2 is
generally a more moderate form with slow progression and onset prior to 10 years of age with skeletal
abnormalities and myopathy. Type 3 is the most severe form with onset in early infancy, skeletal
abnormalities (dysostosis multiplex), and severe central nervous system involvement. Although treatment
is mostly supportive and aimed at preventing complications, hematopoietic stem cell transplant (HSCT)
has been reported to be a feasible therapeutic option. The incidence of alpha-mannosidosis is estimated at
1 in 500,000 live births. An initial diagnostic workup for alpha-mannosidosis includes a multienzyme
screening assay for several oligosaccharidases, including mannosidosis in leukocytes or fibroblasts
(OLIWB / Oligosaccharidases Screen, Leukocytes or OLITC / Oligosaccharidases Screen, Fibroblasts). If
the screening assay is suggestive of alpha-mannosidosis, enzyme analysis of acid alpha-mannosidase can confirm the diagnosis. Sequencing of MAN2B1 allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members.

**Useful For:** Diagnosis of alpha-mannosidosis

**Interpretation:** Deficient activity of this enzyme is consistent with a diagnosis of alpha-mannosidosis.

**Reference Values:**
> or =0.53 nmol/min/mg protein

**Clinical References:**

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**MANN 62511**

**Alpha-Mannosidase, Leukocytes**

**Clinical Information:** Alpha-mannosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid alpha-mannosidase enzyme activity. This enzyme is involved in glycoprotein catabolism, with absent or reduced activity resulting in the accumulation of undigested mannose-containing complex oligosaccharides in the lysosomes, disrupting the normal functioning of cells. Clinical features and severity of symptoms are widely variable within alpha-mannosidosis but, in general, the disorder is characterized by skeletal abnormalities, immune deficiency, hearing impairment, and mental retardation. Three clinical subtypes of the disorder have been described and vary with respect to age of onset and clinical presentation. Type 1 is generally classified by a mild presentation and slow progression with onset after 10 years of age and absence of skeletal abnormalities. Type 2 is generally a more moderate form with slow progression and onset prior to 10 years of age with skeletal abnormalities and myopathy. Type 3 is the most severe form with onset in early infancy, skeletal abnormalities (dyostosis multiplex), and severe central nervous system involvement. Although treatment is mostly supportive and aimed at preventing complications, hematopoietic stem cell transplant has been reported to be a feasible therapeutic option. The incidence of alpha-mannosidosis is estimated at 1 in 500,000 live births. An initial diagnostic workup includes a multienzyme screening assay for several oligosaccharidoses, including mannosidosis in leukocytes or fibroblasts (OLIW / Oligosaccharidoses Screen, Leukocytes or OLITC / Oligosaccharidoses Screen, Fibroblasts). If the screening assay is suggestive of alpha-mannosidosis, enzyme analysis of acid alpha-mannosidase can confirm the diagnosis.

**Useful For:** Diagnosis of alpha-mannosidosis

**Interpretation:** Values <0.54 nmol/min/mg protein are consistent with a diagnosis of alpha-mannosidosis.

**Reference Values:**
> or =0.54 nmol/min/mg protein

**Clinical References:**
Alpha-N-Acetylglucosaminidase, Fibroblasts

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans or GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs, resulting in the clinical features observed in MPS disorders. Sanfilippo syndrome (MPS type III) is an autosomal recessive MPS with 4 recognized types (A-D). Each type is caused by a deficiency in 1 of 4 enzymes involved in the degradation of heparan sulfate resulting in its lysosomal accumulation. Though biochemically different, the clinical presentation of all types is indistinguishable. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but other symptoms seen in MPS, such as coarse facial features and skeletal involvement, tend to be milder. Onset of clinical features usually occurs between 2 and 6 years in a child who previously appeared normal. The presenting symptoms are most commonly developmental delay and severe behavioral problems. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by age 20, though individuals with an attenuated phenotype may have a longer life expectancy. Although there is no cure for Sanfilippo syndrome, research of therapies has included bone marrow transplantation, enzyme replacement, and gene replacement. Sanfilippo syndrome type B is caused by mutations in NAGLU. Diagnostic testing of the coding region of this gene is available as a clinical assay (MP3BZ / Mucopolysaccharidosis IIIB, Full Gene Analysis).

Useful For: Diagnosis of Sanfilippo syndrome, type B (mucopolysaccharidoses, type IIIB)

Interpretation: Deficiency of alpha-N-acetylglucosaminidase is diagnostic for Sanfilippo syndrome type B.

Reference Values:
> or =0.05 nmol/min/mg protein


Alpha-N-Acetylglucosaminidase, Serum

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Sanfilippo syndrome (MPS type III) is an autosomal recessive MPS with 4 recognized types (A-D). Each type is caused by a deficiency in 1 of 4 enzymes involved in the degradation of heparan sulfate resulting in its lysosomal accumulation. Though biochemically different, the clinical presentation of all types is indistinguishable. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but other symptoms seen in MPS, such as coarse facial features and skeletal involvement, tend to be milder. Onset of clinical features usually occurs between 2 and 6 years in a child who previously appeared normal. The presenting symptoms are most commonly developmental delay and severe behavioral problems. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by age 20, although individuals with an attenuated phenotype may have a longer life expectancy. Sanfilippo syndrome type B is due to the absence of the enzyme
N-acetyl-alpha-D-glucosaminidase (alpha-hexosaminidase), caused by mutations in the NAGLU gene. Diagnostic sequencing of the NAGLU gene (MP3BZ / Mucopolysaccharidosis IIIB, Full Gene Analysis) and deletion/duplication studies are available for patients with an enzyme deficiency.

**Useful For:** Preferred assay for diagnosis of Sanfilippo syndrome type B (mucopolysaccharides type IIIB)

**Interpretation:** Deficiency of alpha-N-acetylglucosaminidase is diagnostic for Sanfilippo syndrome type B.

**Reference Values:**
0.09-0.58 U/L

**Clinical References:**

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**ANS 80870**

**Alpha-Naphthyl Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

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**APGH 9003**

**Alpha-Subunit Pituitary Tumor Marker, Serum**

**Clinical Information:** The 3 human pituitary glycoprotein hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotropin (TSH), and the placenta-derived chorionic gonadotropin (hCG), are closely related tropic hormones. They signal through G-protein-coupled receptors, regulating the hormonal activity of their respective endocrine target tissues. Each is composed of an alpha- and a beta-subunit, coupled by strong noncovalent bonds. The alpha-subunits of all 4 hormones are essentially identical (92 amino acids; molecular weight [MW] of the "naked" protein:10,205 Da), being transcribed from the same gene and showing only variability in glycosylation (MW of the glycosylated proteins:13,000-18,000 Da). The alpha-subunits are essential for receptor transactivation. By contrast, all the different beta-subunits are transcribed from separate genes, show less homology, and convey the receptor specificity of the dimeric hormones. Under physiological conditions, alpha- and beta-chain synthesis and secretions are tightly coupled, and only small amounts of monomeric subunits are secreted. However, under certain conditions, coordinated production of intact glycoprotein hormones may be disturbed and disproportionate quantities of free alpha-subunits are secreted. In particular, some pituitary adenomas may overproduce alpha-subunits. Although most commonly associated with gonadotroph- or thyrotroph-derived tumors, alpha-subunit secretion has also been observed in corticotroph, lactotroph, and somatotroph pituitary adenomas. Overall, depending on cell type and tumor size, between 5% to 30% of pituitary adenomas will produce sufficient free alpha-subunits to result in elevated serum levels, which usually fall with successful treatment. Stimulation testing with hypothalamic releasing factors (eg, gonadotropin releasing hormone [GnRH] or thyrotropin-releasing hormone [TRH]) may result in further elevations, disproportionate to those seen in individuals without tumors. Measurement of free alpha-subunit after GnRH-stimulation testing can also be useful in the differential diagnosis of constitutional delay of puberty (CDP) versus hypogonadotrophic hypogonadism (HH). CDP is a benign, often familial, condition in which puberty onset is significantly delayed, but eventually occurs, and then proceeds normally. By contrast, HH represents a disease state characterized by lack of gonadotropin production. Its causes are varied, including hypothalamic and pituitary inflammatory or neoplastic
disorders, a range of specific genetic abnormalities, as well as unknown causes. In children, HH results in complete failure to enter puberty without medical intervention. In children with CDP, in normal pubertal children, in normal adults and, to a lesser degree, in normal prepubertal children, GnRH administration results in increased serum LH, FSH, and alpha-subunit levels. This response is greatly attenuated in patients with HH, particularly with regard to the post-GnRH rise in alpha-subunit concentrations.

**Useful For:** Adjunct in the diagnosis of pituitary tumors As part of the follow-up of treated pituitary tumor patients Differential diagnosis of thyrotropin-secreting pituitary tumor versus thyroid hormone resistance Differential diagnosis of constitutional delay of puberty versus hypogonadotrophic hypogonadism

**Interpretation:** In the case of pituitary adenomas that do not produce significant amounts of intact tropic hormones, diagnostic differentiation between sellar- and tumors of nonpituitary origin (eg, meningiomas or craniopharyngiomas) can be difficult. In addition, if such nonsecreting adenomas are very small, then they can be difficult to distinguish from physiological pituitary enlargements. In a proportion of these cases, free alpha-subunit may be elevated, aiding in diagnosis. Overall, 5% to 30% of pituitary adenomas produce measurable elevation in serum free alpha-subunit concentrations. There is also evidence that an exuberant free alpha-subunit response to thyrotropin-releasing hormone (TRH) administration may occur in some pituitary adenoma patients that do not have elevated baseline free alpha-subunit levels. A more than 2-fold increase in free alpha-subunit serum concentrations at 30 to 60 minutes following intravenous administration of 500 mcg of TRH is generally considered abnormal, but some investigators consider any increase of serum free alpha-subunit that exceeds the reference range as abnormal. TRH testing is not performed in the laboratory, but in specialized clinical testing units under the supervision of a physician. In pituitary tumors patients with pre-treatment elevations of serum free alpha-subunit, successful treatment is associated with a reduction of serum free alpha-subunit levels. Failure to lower levels into the normal reference range may indicate incomplete cure, and secondary rises in serum free alpha-subunit levels can indicate tumor recurrence. Small thyrotropin (TSH)-secreting pituitary tumors are difficult to distinguish from thyroid hormone resistance. Both types of patients may appear clinically euthyroid or mildly hyperthyroid and may have mild-to-modest elevations in peripheral thyroid hormone levels along with inappropriately (for the thyroid hormone level) detectable TSH, or mildly-to-modestly elevated TSH. Elevated serum free alpha-subunit levels in such patients suggest a TSH secreting tumor, but mutation screening of the thyroid hormone receptor gene may be necessary for a definitive diagnosis. Constitutional delay of puberty (CDP), is a benign, often familial condition, in which puberty onset is significantly delayed, but eventually occurs and then proceeds normally. By contrast, hypogonadotrophic hypogonadism (HH) represents a disease state characterized by lack of gonadotropin production. Its causes are varied, ranging from idiopathic over specific genetic abnormalities to hypothalamic and pituitary inflammatory or neoplastic disorders. In children, it results in complete failure to enter puberty without medical intervention. CDP and HH can be extremely difficult to distinguish from each other. Intravenous administration of 100 mcg gonadotropin releasing hormone (GnRH) results in much more substantial rise in free alpha-subunit levels in CDP patients, compared with HH patients. A >6-fold rise at 30 or 60 minutes post-injection is seen in >75% of CDP patients, while a <2-fold rise appears diagnostic of HH. Increments between 2-fold and 6-fold are nondiagnostic. GnRH testing is not performed in the laboratory, but in specialized clinical testing units under the supervision of a physician.

**Reference Values:**

**PEDIATRIC**
- < or =5 days: < or =50 ng/mL
- 6 days-12 weeks: < or =10 ng/mL
- 3 months-17 years: < or =1.2 ng/mL
- Tanner II-IV*: < or =1.2 ng/mL

**ADULTS**
- Males: < or =0.5 ng/mL
- Premenopausal females: < or =1.2 ng/mL
- Postmenopausal females: < or =1.8 ng/mL

Pediatric and adult reference values based on Mayo studies.

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of
11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

**Clinical References:**

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**63129 Alport (Collagen IV Alpha 5 and Alpha 2) Immunofluorescent Stain, Renal**

**Clinical Information:** Alport syndrome is a hereditary disease of basement membrane collagen type IV. Mutations in collagen IV alpha genes cause characteristic abnormal immunofluorescence staining patterns within the glomerular basement membrane. Alport syndrome is characterized by hematuria, proteinuria, progressive renal failure, and high-tone sensorineural hearing loss.

**Useful For:** Assisting in the diagnosis of hereditary nephritis (Alport syndrome)

**Interpretation:** This test, (when not accompanied by a pathology consultation request) will be reported as: 1) normal pattern, 2) consistent with X-linked hereditary nephritis, or 3) consistent with autosomal hereditary nephritis. If additional interpretation or analysis is needed, request 70012 / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.

**Reference Values:**
Reporting of immunofluorescent (IF) double staining for alpha 2 and alpha 5 chains of type IV collagen on kidney biopsies:

1) Normal pattern of staining (ie, preserved linear alpha 5 staining of glomerular basement membranes, Bowman capsule, and distal tubular basement membranes). This pattern of staining is seen in normal individuals and patients with thin glomerular basement membrane disease but does not exclude the diagnosis of hereditary nephritis/Alport syndrome.

2) Consistent with X-linked hereditary nephritis (Alport syndrome). There is global or segmental loss of alpha 5 staining of glomerular basement membranes, Bowman capsule, and distal tubular basement membranes. This pattern of loss of staining is usually due to mutations in the COL4A5 gene on the X chromosome.

3) Consistent with autosomal hereditary nephritis (Alport syndrome). There is global or segmental loss of alpha 5 staining of glomerular basement membranes but preserved alpha 5 staining of Bowman capsule and distal tubular basement membranes. This pattern of loss of staining is usually due to mutations in the COL4A3 or COL4A4 genes on chromosome 2.

4) No interpretation can be reported if the specimen contains no intact glomeruli.

Reporting of IF double staining for alpha 2 and alpha 5 chains of type IV collagen on skin biopsies:

1) Normal pattern of staining (ie, preserved linear alpha 5 staining of epidermal basement membranes). This pattern of staining is seen in normal individuals and patients with thin glomerular basement membrane disease but does not exclude the diagnosis of hereditary nephritis/Alport syndrome.

2) Consistent with X-linked hereditary nephritis (Alport syndrome). There is global or segmental loss of alpha 5 staining of epidermal basement membranes but preserved alpha 5 staining of Bowman capsule and distal tubular basement membranes. This pattern of loss of staining is usually due to mutations in the COL4A5 gene on the X chromosome.

3) No interpretation can be reported if the biopsy contains no epidermis.
Notes:

1) Approximately one-third of patients with established hereditary nephritis based on typical ultrastructural findings and family history show loss of glomerular basement membrane or epidermal basement membrane staining for the alpha 5 chain of type IV collagen. Therefore, a normal staining pattern does not exclude the diagnosis of hereditary nephritis.

2) In patients with hereditary nephritis, preserved alpha 5 staining indicates small mutations (eg, missense, splice site) and is generally associated with a better renal outcome, while loss of alpha 5 staining indicates larger mutations (eg, deletion, nonsense, frame-shift) and a worse renal outcome.

3) Because alpha 3 and alpha 4 chains of type IV collagen are not expressed in the epidermal basement membranes, patients with autosomal hereditary nephritis have preserved staining for alpha 5 on epidermal basement membranes and, therefore, skin biopsy cannot exclude autosomal hereditary nephritis.


**Clinical References:**


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**FALPX**

**Alprazolam (Xanax)**

**Reference Values:**

5 – 25 ng/mL

Reporting Limit: 2.0 ng/mL

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**ALTN**

**Alternaria tenuis, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L | Interpretation
--- | ---
0 | Negative
1 | 0.35-0.69 | Equivocal
2 | 0.70-3.49 | Positive
3 | 3.50-17.4 | Positive
4 | 17.5-49.9 | Strongly positive
5 | 50.0-99.9 | Strongly positive
6 | > or =100 | Strongly positive

Reference values apply to all ages.


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**ALU 8828**

**Aluminum, 24 Hour, Urine**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in RF patients: - Aluminum-laden dialysis water can expose dialysis patients to aluminum.
- Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate.
- The dialysis process is not highly effective at eliminating aluminum.
- Aluminum-laden phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring aluminum exposure Monitoring metallic prosthetic implant wear

**Interpretation:** Daily excretion >20 mcg/specimen indicates exposure to excessive amounts of aluminum. In renal failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal. Prosthetic wear is known to result in increased circulating concentration of metal ions. Modest increase (10-20 mcg/specimen) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations >50 mcg/specimen in a patient with an aluminum-based implant, not undergoing dialysis, suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**

0-20 mcg/specimen

Reference values apply to all ages.

**Clinical References:** 1. Oâ€™Shea S, Johnson DW: Review article: addressing risk factors in

**Aluminum, Random, Urine**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in RF patients: - Aluminum-laden dialysis water can expose dialysis patients to aluminum. - Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. - The dialysis process is not highly effective at eliminating aluminum. - Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring aluminum exposure when a 24-hour urine cannot be collected Monitoring metallic prosthetic implant wear when a 24-hour urine cannot be collected

**Interpretation:** Daily excretion >20 mcg/L indicates exposure to aluminum. Prosthesis wear is known to result in increased circulating concentration of metal ions. (1) Modest increase (10-20 mcg/specimen) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations >50 mcg/specimen in a patient with an aluminum-based implant, not undergoing dialysis, suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. In renal failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal.

**Reference Values:**
0-20 mcg/L
Reference values apply to all ages.


**Aluminum, Serum**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in RF patients: - Aluminum-laden dialysis water can expose dialysis patients to aluminum. - Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. - The
dialysis process is not highly effective at eliminating aluminum. Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood, where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Deposition of aluminum in bone also interrupts normal calcium exchange. The calcium in bone becomes unavailable for resorption back into blood under the physiologic control of parathyroid hormone (PTH) and results in secondary hyperparathyroidism. While PTH is typically quite elevated in RF, 2 different processes may occur: 1) High-turnover bone disease associated with high PTH (>150 pg/mL) and relatively low aluminum (<20 ng/mL), or 2) low-turnover bone disease with lower PTH (<50 pg/mL) and high aluminum (>60 ng/mL). Low-turnover bone disease indicates aluminum intoxication. Serum aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Preferred monitoring for aluminum toxicity in patients undergoing dialysis. Preferred test for routine aluminum screening. Monitoring metallic prosthetic implant wear.

**Interpretation:** Patients in renal failure not receiving dialysis therapy invariably have serum aluminum levels above the 60 ng/mL range. McCarthy(1) and Hernandez(2) describe a biochemical profile that is characteristic of aluminum overload disease in dialysis patients: -Patients in renal failure with no signs or symptoms of osteomalacia or encephalopathy usually had serum aluminum <20 ng/mL and parathyroid hormone (PTH) concentrations >150 pg/mL, which is typical of secondary hyperparathyroidism. -Patients with signs and symptoms of osteomalacia or encephalopathy had serum aluminum >60 ng/mL and PTH concentrations <50 pg/mL (PTH above the reference range, but low for secondary hyperparathyroidism). -Patients who had serum aluminum >60 ng/mL and <100 ng/mL were identified as candidates for later onset of aluminum overload disease that required aggressive efforts to reduce their daily aluminum exposure. This was done by switching them from aluminum-containing phosphate binders to calcium-containing phosphate binders, by ensuring that their dialysis water had <10 ng/mL of aluminum, and ensuring the albumin used during postdialysis therapy was aluminum-free. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (6-10 ng/mL) in serum aluminum concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations >10 ng/mL in a patient with an aluminum-based implant not undergoing dialysis suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
- 0-6 ng/mL (all ages)
- <60 ng/mL (dialysis patients-all ages)

**Clinical References:**
skeletal muscle differentiation. They can be divided into 3 subtypes: alveolar, embryonal, and pleomorphic. The rarer alveolar rhabdomyosarcomas (ARMS) are seen in older children, are more likely to occur in limbs, and are associated with higher stage disease and an unfavorable prognosis. The alveolar form consists of 2 variants; classic and solid. The classic form is characterized by small round cells with dark hyperchromatic nuclei containing distinct nucleoli, held together by strands of intercellular collagen, thereby creating a cellular architecture resembling the alveolar spaces of the lungs. The solid form is characterized by a similar cellular morphology but without the formation of alveolar spaces. ARMS are also members of the small round cell tumor group that includes synovial sarcoma, lymphoma, Wilms tumor, Ewing sarcoma, and desmoplastic small round cell tumor. Most cases of ARMS (75%) are associated with a t(2;13)(q35;q14), where a chimeric gene is formed from the rearrangement of the PAX3 gene on chromosome 3 and the FOXO1(FKHR) gene on chromosome 13. A small subset of ARMS patients (10%) are associated with a variant translocation, t(1;13)(q36;q14), involving the PAX1 gene of chromosome 1 and the FOXO1 gene. Detection of these transcripts by RT-PCR (ARMS, Alveolar Rhabdomyosarcomas, RT-PCR), which allows specific identification of the t(2;13) and t(1;13), has greatly facilitated the diagnosis of ARMS tumors. FISH analysis (using the FOXO1(FKHR) probe) adds the ability to detect variant FOXO1 rearrangements not detectible by PCR, and will often yield results when the quality of the available RNA is poor or the PCR results are equivocal.

**Useful For:** Supporting the diagnosis of alveolar rhabdomyosarcomas (ARMS) when used in conjunction with an anatomic pathology consultation. Aids in the diagnosis of ARMS when reverse transcriptase-PCR results are equivocal or do not support the clinical picture.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FOXO1 FISH probe. A positive result suggests rearrangement of the FOXO1 gene region at 13q14 and is consistent with a subset of alveolar rhabdomyosarcomas (ARMS). A negative result suggests FOXO1 gene rearrangement is not present, but does not exclude the diagnosis of alveolar rhabdomyosarcomas (ARMS).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. Fletcher CDM, Unni K, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC: Lyon 2002, pp 150-152
pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas and are useful in the diagnosis of these lesions. Most cases of ARMS have a t(2;13)(q35;q14) reciprocal translocation. This rearrangement juxtaposes 5’ portions of the PAX3 gene on chromosome 2 with 3’ portion of the FOXO1 gene on chromosome 13 resulting in a chimeric gene in the designated chromosome 13 that encodes a transcriptional regulatory protein in 75% of cases. Another variant t(1;13)(q36;q14) translocation fuses the 5’ portion of the PAX7 gene on chromosome 1 with the FOXO1 gene on chromosome 13 in a smaller number of cases (10%). The PAX3-FOXO1 fusion is associated with a worse prognosis than the PAX7-FOXO1 fusion.

**Useful For:** Supporting the diagnosis of alveolar rhabdomyosarcoma

**Interpretation:** A positive PAX3-FOXO1 or PAX7-FOXO1 result is consistent with a diagnosis of alveolar rhabdomyosarcoma (ARMS). Sarcomas other than ARMS, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of ARMS.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
2. Ladanyi M, Bridge JA: Contribution of molecular genetic data to the classification of sarcomas. Hum Pathol 2000;31:532-538

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**TFE3F 35319**

**Alveolar Soft Part Sarcoma (ASPS)/Renal Cell Carcinoma (RCC), Xp11.23 (TFE3), FISH, Tissue**

**Clinical Information:** Alveolar soft-part sarcoma (ASPS) is a rare malignant tumor typically occurring in patients in their 20s to 30s within the muscle and deep tissues of the extremities. ASPS is slow growing and refractory to chemotherapy with a propensity to metastasize. Prolonged survival is possible even with metastasis, although the long-term disease-related mortality rate is high. ASPS is characterized by a translocation that results in fusion of TFE3 on chromosome Xp11.2 with ASPSCR1 (also called ASPL or RCC17) on chromosome 17q25.3. Both balanced and unbalanced forms (loss of the derivative X chromosome) of the translocation have been observed. Another tumor, a rare subset of papillary renal cell carcinoma (RCC) with a distinctive pathologic morphology, has rearrangements of TFE3 with ASPSCR1 or other fusion partner genes. This tumor predominantly affects children and young adults, presents at an advanced stage but with an indolent clinical course, and is a distinct entity in the World Health Organization classification. Typically a balanced form of the translocation is present in the RCC variant. An assay to detect rearrangement of TFE3 is useful to resolve diagnostic uncertainty in these tumor types, as immunohistochemistry for TFE3 is not reliable.

**Useful For:** An aid in the diagnosis of alveolar soft-part sarcoma or renal cell carcinoma variant when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of nuclei with the abnormality exceeds the established normal cutoff for the TFE3 probe set. A positive result of TFE3 rearrangement is consistent with a diagnosis of alveolar soft-part sarcoma (ASPS) or renal cell carcinoma (RCC) variant. A negative result suggests that TFE3 is not rearranged, but does not exclude the diagnosis of ASPS or RCC variant.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**FAMAN 91132**

**Amantadine (Symmetrel)**

**Reference Values:**

Units: ng/mL

Therapeutic range has not been established.

Expected steady state amantadine concentrations in patients receiving recommended daily dosages:

- 200-1000 ng/mL
- Toxicity reported at greater than 2000 ng/mL

**PAMIK 37032**

**Amikacin, Peak, Serum**

**Clinical Information:** Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

**Useful For:** Monitoring adequacy of serum concentration during amikacin therapy

**Interpretation:** For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if the peak serum concentration is maintained >35.0 mcg/mL for a prolonged period of time.

**Reference Values:**

- Peak: 20.0-35.0 mcg/mL
- Toxic peak: >40.0 mcg/mL

**Clinical References:**


**RAMIK 37033**

**Amikacin, Random, Serum**

**Clinical Information:** Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which
may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

**Useful For:** Monitoring adequacy of blood concentration during amikacin therapy

**Interpretation:** For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if, for prolonged periods of time, peak serum concentrations are maintained >35.0 mcg/mL, or trough concentrations are maintained at >10.0 mcg/mL.

**Reference Values:**
- Peak: 20.0-35.0 mcg/mL
- Toxic peak: >40.0 mcg/mL
- Trough: <8.0 mcg/mL
- Toxic trough: >10.0 mcg/mL

**Clinical References:**

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**TAMIK 37031**

**Amikacin, Trough, Serum**

**Clinical Information:** Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

**Useful For:** Monitoring adequate clearance of amikacin near the end of a dosing cycle

**Interpretation:** For conventional (nonpulse) dosing protocols, trough concentrations should fall to <8.0 mcg/mL. Toxicity may occur if the trough serum concentration is maintained >10.0 mcg/mL for prolonged periods of time.

**Reference Values:**
- Trough: <8.0 mcg/mL
- Toxic trough: >10.0 mcg/mL

**Clinical References:**

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**AAMSD 60200**

**Amino Acids, Maple Syrup Urine Disease Panel, Plasma**

**Clinical Information:** Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). MSUD patients can be divided into 5 phenotypes: classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3)-deficient depending on the clinical
presentation and response to thiamine administration. Classic MSUD which is the most common and most severe form, presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor to urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Age of onset for individuals with variant forms of MSUD is variable and some have initial symptoms as early as 2 years of age. Symptoms include poor growth and feeding, irritability, and developmental delays. These patients can also experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress. MSUD is a panethnic condition, but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1:760 live births. The incidence of MSUD is approximately 1:185,000 live births in the general population. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and allo-isoleucine concentrations. Orthotopic liver transplantation has been used with success and is an effective therapy for MSUD.

Useful For: Follow-up of patients with maple syrup urine disease Monitoring of dietary compliance for patients with maple syrup urine disease

Interpretation: The quantitative results of isoleucine, leucine, valine, and allo-isoleucine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

Reference Values:

ISOLEUCINE
< or =23 months: 31-105 nmol/mL
2-17 years: 30-111 nmol/mL
> or =18 years: 36-107 nmol/mL

LEUCINE
< or =23 months: 48-175 nmol/mL
2-17 years: 51-196 nmol/mL
> or =18 years: 68-183 nmol/mL

VALINE
< or =23 months: 83-300 nmol/mL
2-17 years: 106-320 nmol/mL
> or =18 years: 136-309 nmol/mL

ALLO-ISOLEUCINE
< or =23 months: <2 nmol/mL
2-17 years: <3 nmol/mL
> or =18 years: <5 nmol/mL

in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and death. Treatment for amino acid disorders includes very specific dietary modifications. Nonessential amino acids are synthesized by the body, while essential amino acids are not and must be obtained through an individual's diet. Therapeutic diets are coordinated and closely monitored by a dietician and/or physician. They are structured to provide the necessary balance of amino acids with particular attention to essential amino acids and those which accumulate in a particular disorder. Patients must pay close attention to the protein content in their diet and generally need to supplement with medical formulas and foods. Dietary compliance is monitored by periodic analysis of plasma amino acids. In addition, plasma amino acid analysis may have clinical importance in the evaluation of several acquired conditions including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns.

**Useful For:** Evaluating patients with possible inborn errors of metabolism May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Plasma Amino Acid Reference Values (nmol/mL) Age Groups</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>(n=191) 2-17 Years (n=441) &gt; or =18 Years (n=148)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphoserine (PSer)</td>
<td></td>
<td></td>
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<tr>
<td>Phosphoethanolamine (PEtN)</td>
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<td></td>
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<tr>
<td>Taurine (Tau)</td>
<td>37-177</td>
<td>38-153</td>
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<td>Asparagine (Asn)</td>
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<td>29-87</td>
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<td>Serine (Ser)</td>
<td>69-271</td>
<td>71-208</td>
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<td>Hydroxyproline (Hyp)</td>
<td>8-61</td>
<td>7-35</td>
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<td>Glycine (Gly)</td>
<td>111-426</td>
<td>149-417</td>
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<td>Glutamine (Gln)</td>
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<td>Histidine (His)</td>
<td>10-116</td>
<td>12-132</td>
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<td>Threonine (Thr)</td>
<td>47-237</td>
<td>58-195</td>
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### Amino Acids

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### Clinical References

intolerance and Hartnup disease, as well as in conditions with renal tubular dysfunction including Lowe syndrome and Dent disease.

**Useful For:** Evaluating patients with possible inborn errors of metabolism May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

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**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism that affect amino acid transport and metabolism have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and death. Cerebrospinal fluid (CSF) specimens are highly informative for a subset of these conditions, such as nonketotic hyperglycinemia and serine biosynthesis defects. CSF specimens are most informative when a plasma specimen is drawn at the same time and the ratio of the amino acid concentrations in CSF to plasma is calculated.

**Useful For:** Evaluating patients with possible inborn errors of amino acid metabolism, in particular nonketotic hyperglycinemia and serine biosynthesis defects, especially when used in conjunction with concomitantly drawn plasma specimens

**Interpretation:** When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is provided. This interpretation includes an overview of the results and their significance, a correlation to available clinical information,
elements of differential diagnosis, and recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere, and the telephone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

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<tr>
<td>Methionine (Met)</td>
<td>14-61 9-28 8-20 11-40</td>
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<tr>
<td>Valine (Val)</td>
<td>14-61 9-28 8-20 11-40</td>
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<tr>
<td>Tyrosine (Tyr)</td>
<td>8-83 5-24 5-17</td>
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<tr>
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<tr>
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<td>12-41 6-21 7-16 7-29</td>
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<tr>
<td>Leucine (Leu)</td>
<td>12-41 6-21 7-16 7-29</td>
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<tr>
<td>Phenylalanine (Phe)</td>
<td>7-40 5-18 7-21</td>
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<tr>
<td>Tryptophan (Trp)</td>
<td>7-40 5-18 7-21</td>
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<tr>
<td>Allo-isoleucine (AlloIle)</td>
<td>7-40 5-18 7-21</td>
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</table>


**AAUCD Amino Acids, Urea Cycle Disorders Panel, Plasma**

**Clinical Information:** Urea cycle disorders (UCD) are a group of inherited disorders of nitrogen detoxification that result when any of the enzymes in the urea cycle (carbamoylphosphate synthetase I [CPS I]; ornithine transcarbamylase [OTC]; argininosuccinic acid synthetase; argininosuccinic acid lyase; arginase; or the cofactor producer, N-acetyl glutamate synthetase [NAGS]), have deficient or reduced activity. The urea cycle serves to break down nitrogen and defects in any of the steps of the pathway can result in an accumulation of ammonia, which can be toxic to the nervous system. Infants with a complete enzyme deficiency typically appear normal at birth, but present in the neonatal period as ammonia levels rise with lethargy, seizures, hyper- or hypoventilation, and ultimately coma or death. Individuals with partial enzyme deficiency may present later in life, typically following an acute illness or other stressor. Symptoms may be less severe and may present with episodes of psychosis, lethargy, cyclical vomiting, and behavioral abnormalities. All of the UCDs are inherited as autosomal recessive disorders, with the exception of OTC deficiency, which is X-linked. UCDs may be suspected with elevated ammonia, normal anion gap, and a normal glucose. Plasma amino acids can be used to aid in the diagnosis of a UCD. Measurement of urinary orotic acid, enzyme activity (CPS I, OTC, or NAGS), and molecular genetic testing can help to distinguish the conditions and allows for diagnostic confirmation. Acute treatment for UCDs consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, orthotopic liver transplantation has been used with success in treating some patients.

**Useful For:** Differential diagnosis and follow-up of patients with urea cycle disorders

**Interpretation:** The quantitative results of glutamine, ornithine, citrulline, arginine, and argininosuccinic acid with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

**Reference Values:**

**GLUTAMINE**

- ≤23 months: 316-1020 nmol/mL
- 2-17 years: 329-976 nmol/mL
- > or =18 years: 371-957 nmol/mL
ORNITHINE
< or =23 months: 20-130 nmol/mL
2-17 years: 22-97 nmol/mL
> or =18 years: 38-130 nmol/mL

CITRULLINE
< or =23 months: 9-38 nmol/mL
2-17 years: 11-45 nmol/mL
> or =18 years: 17-46 nmol/mL

ARGININE
< or =23 months: 29-134 nmol/mL
2-17 years: 31-132 nmol/mL
> or =18 years: 32-120 nmol/mL

ARGININOSUCCINIC ACID
<2 nmol/mL
Reference value applies to all ages.

Clinical References:

ALAUR
61547
Aminolevulinic Acid (ALA), Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrrias. The porphyrrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: aminolevulinic acid dehydratase deficiency porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. The excretion of aminolevulinic acid (ALA) can be increased due to one of the inherited acute porphyrrias or due to secondary inhibition of ALA dehydratase. Among the secondary causes, acute lead intoxication results in the highest degree of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication, tyrosinemia type I, alcoholism, and pregnancy. The work up of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

Useful For: Assistance in the differential diagnosis of the various acute hepatic porphyrias

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional
questions.

Reference Values:
<1 year: < or =10 nmol/mL
1-17 years: < or =20 nmol/mL
> or =18 years: < or =15 nmol/mL


### Aminolevulinic Acid (ALA), Urine

**Reference Values:**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Units</th>
<th>Ref Interval</th>
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</thead>
<tbody>
<tr>
<td>Creatinine, Urine â€“ mg/dL</td>
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<td></td>
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<tr>
<td>Creatinine, Urine-mg/day</td>
<td>mg/d</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
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<th>Female</th>
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<tbody>
<tr>
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<tr>
<td>9-12 years</td>
<td>300-1300</td>
<td>300-1300</td>
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<tr>
<td>13-17 years</td>
<td>500-2300</td>
<td>400-1600</td>
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<tr>
<td>18-50 years</td>
<td>1000-2500</td>
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<td>800-2100</td>
<td>500-1400</td>
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<tr>
<td>81 years and older</td>
<td>600-2000</td>
<td>400-1300</td>
</tr>
<tr>
<td>Aminolevulinic Acid umol/L</td>
<td>umol/L</td>
<td>0-35</td>
</tr>
<tr>
<td>Aminolevulinic Acid umol/day</td>
<td>umol/d</td>
<td>0-60</td>
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</tbody>
</table>

### Aminolevulinic Acid Dehydratase (ALA-D), Washed Erythrocytes

**Clinical Information:** Porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen (PBG) remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive, acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 7 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria
Useful For: Confirmation of a diagnosis of aminolevulinic acid dehydratase deficiency porphyria. Due to limited stability for this test, the preferred test for analysis of ALAD is ALAD / Aminolevulinic Acid Dehydratase (ALAD), Whole Blood. This test will not detect lead intoxication.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
Reference ranges have not been established for patients who are <16 years of age.

> or =4.0 nmol/L/sec
3.5-3.9 nmol/L/sec (indeterminate)
<3.5 nmol/L/sec (diminished)

Clinical References:

ALAD
Aminolevulinic Acid Dehydratase (ALAD), Whole Blood

Clinical Information: Porphyrinas are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen (PBG) remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive, acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 7 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

Useful For: This test is the preferred test for the confirmation of a diagnosis of aminolevulinic acid dehydratase deficiency porphyria. This test will not detect lead intoxication.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
Reference ranges have not been established for patients who are <16 years of age.

> or =4.0 nmol/L/sec
3.5-3.9 nmol/L/sec (indeterminate)
<3.5 nmol/L/sec (diminished)


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**Amiodarone, Serum**

**Clinical Information:** Amiodarone is an antiarrhythmic agent used to treat life-threatening arrhythmias; it is typically categorized as a Class III drug (antiarrhythmic agents that are potassium channel blockers) but shows several mechanisms of action. The U.S. Food and Drug Administration approved the use of amiodarone for recurrent ventricular fibrillation and recurrent, hemodynamically unstable ventricular tachycardia only after demonstrating lack of response to other antiarrhythmics, but more recent studies have shown amiodarone to be the antiarrhythmic agent of choice for many situations, including atrial fibrillation.(1) Amiodarone can be administered orally or intravenously for cardiac rhythm control. It is 95% protein bound in blood, with a volume of distribution of 60 L/kg. Amiodarone elimination is quite prolonged, with a mean half-life of 53 days. CYP3A4 converts amiodarone to its equally active metabolite, N-desethylamiodarone (DEA), which displays very similar pharmacokinetics and serum concentrations, compared to the parent drug. (2) Current therapeutic ranges are based solely on amiodarone, but most individuals will have roughly equivalent concentrations of DEA at steady state.(3) Numerous side effects have been associated with amiodarone. The most common adverse effect is disruption of thyroid function (hypo- or hyperthyroidism) due to amiodarone’s structural similarity to thyroid hormones. Neurological and gastrointestinal toxicities are concentration-dependent, whereas thyroid dysfunction, pulmonary fibrosis, and hepatotoxicity are more loosely linked to drug concentration. There is significant potential for drug interactions involving amiodarone, including several other cardioactive drugs (eg, digoxin, verapamil, class I antiarrhythmics [sodium channel blockers]), warfarin, statins, and CYP3A4 substrates.

**Useful For:** Monitoring amiodarone therapy, especially when amiodarone is coadministered with other drugs that may interact Evaluation of possible amiodarone toxicity Assessment of patient compliance

**Interpretation:** Clinical effects generally require serum concentrations >0.5 mcg/mL. Increased risk of toxicity is associated with amiodarone concentrations >2.5 mcg/mL. Although therapeutic and toxic ranges are based only on the parent drug, the active metabolite N-desethylamiodarone should be present in similar concentrations to amiodarone.

**Reference Values:**

**AMIODARONE**

Therapeutic concentration: 0.5-2.0 mcg/mL

Toxic concentration: >2.5 mcg/mL

**DESETHYLAMIODARONE**

No therapeutic range established; activity and serum concentration are similar to parent drug.


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Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 123
**Amitriptyline and Nortriptyline, Serum**

**Clinical Information:** Amitriptyline is a tricyclic antidepressant that is metabolized to nortriptyline, which has similar pharmacologic activity. The relative blood levels of amitriptyline and nortriptyline are highly variable among patients. Amitriptyline is the drug of choice in treatment of depression when the side effect of mild sedation is desirable. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage. Amitriptyline displays major cardiac toxicity when the concentration of amitriptyline and nortriptyline is in excess of 300 ng/mL, characterized by QRS widening leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect; blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is in excess of 300 ng/mL, characterized by QRS widening leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to amitriptyline when combined serum levels of amitriptyline and nortriptyline are between 80 and 200 ng/mL. Risk of toxicity is increased with combined levels > or =300 ng/mL. Most individuals display optimal response to nortriptyline with serum levels between 70 and 170 ng/mL. Risk of toxicity is increased with nortriptyline levels > or =300 ng/mL. Some individuals may respond well outside of these ranges, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

**AMITRIPTYLINE AND NORTRIPTYLINE**
- Total therapeutic concentration: 80-200 ng/mL

**NORTRIPTYLINE ONLY**
- Therapeutic concentration: 70-170 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**

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**Ammonia, Plasma**

**Clinical Information:** Ammonia is a waste product of protein catabolism; it is potentially toxic to the central nervous system. Increased plasma ammonia may be indicative of hepatic encephalopathy, hepatic coma in terminal stages of liver cirrhosis, hepatic failure, acute and subacute liver necrosis, and Reyeâ€™s syndrome. Hyperammonemia may also be found with increasing dietary protein intake. The major cause of hyperammonemia in infants includes inherited deficiencies of urea cycle enzymes, inherited metabolic disorders of organic acids and the dibasic amino acids lysine and ornithine, and severe liver disease.

**Useful For:** Assisting in the diagnosis of hepatic coma Investigating and monitoring treatment for inborn errors of metabolism Evaluating patients with advanced liver disease

**Interpretation:** Plasma ammonia concentrations do not correlate well with the degree of hepatic encephalopathy. Elevated ammonia concentration may also be found with increased dietary protein intake.
intake.

**Reference Values:**
< or = 30 mcmol/L


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### Ammonium, 24 Hour, Urine

**Clinical Information:** The kidney regulates acid excretion and systemic acid base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients. The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: 1. High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. 2. Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. 3. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base) this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient.

**Useful For:** Diagnosis of the cause of an acidosis Diagnosis and treatment of kidney stones

**Interpretation:** If a patient has an acidosis, and the amount of ammonium in the urine is low, this suggests a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

**Reference Values:**
15-56 mmol/24 hr
Reference values have not been established for patients <18 years and >77 years of age. Reference values apply to 24 hour collections.

**Clinical References:**

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### Ammonium, Random, Urine

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile, Pediatric, Random, Urine.
Rambo, Random, Urine

**Clinical Information:** The kidney regulates acid excretion and systemic acid-base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus measuring the urine ammonium level can provide understanding of the cause of an acid-base disturbance in individual patients. (1-3) The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual’s acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. -Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base) this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. (4)

**Useful For:** Diagnosis of the cause of an acidosis Diagnosis and treatment of kidney stones

**Interpretation:** If a patient has an acidosis, and the amount of ammonium in the urine is low, this suggests a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

**Reference Values:**
Random: 3-65 mmol/L
No reference values established for <18 years and >77 years of age.

**Clinical References:**

Culaf, 35244

Amniotic Fluid Culture for Genetic Testing

**Clinical Information:** Fetal cells obtained by amniocentesis (amniocytes) are used for a wide range of laboratory tests. Prior to testing, the cells may need to be cultured to obtain adequate numbers of amniocytes.

**Useful For:** Producing amniocyte cultures that can be used for genetic analysis Once confluent flasks are established, the amniocyte cultures are sent to other laboratories, either within Mayo Clinic or to external sites, based on the specific testing requested.

**Reference Values:**
Not applicable


Amobs, Current as of July 8, 2016 11:28 am CDT

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Amobarbital, Serum

Clinical Information: Amobarbital is an intermediate-acting barbiturate with hypnotic properties used in short-term treatment of insomnia and to reduce anxiety and provide sedation preoperatively.\(^{(1,2)}\) Amobarbital is administered by intravenous infusion or intramuscular injection. The duration of its hypnotic effect is about 6 to 8 hours. The drug distributes throughout the body, with a volume of distribution of 0.9 to 1.4 L/kg, and about 59% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. Its half-life is about 15 to 40 hours (mean: 25 hours). Excretion occurs mainly in the urine.\(^{(2,3)}\)

Useful For: Monitoring amobarbital therapy

Interpretation: The therapeutic range of amobarbital is 1 to 5 mcg/mL, with toxicity typically associated with concentrations >10 mcg/mL.\(^{(2)}\)

Reference Values:
- Therapeutic concentration: 1.0-5.0 mcg/mL
- Toxic concentration: >10.0 mcg/mL
- Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.


Amoxapine (Asendin) and 8-Hydroxyamoxapine

Reference Values:
- Amoxapine: No reference range provided ng/mL
- 8-Hydroxyamoxapine: No reference range provided ng/mL
- Combined Total: 200 ìg to 400 ng/mL

Amoxicillin, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:


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### AMPD 82049

**AMP Deaminase ST**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

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### FAMP 91171

**Amphetamine, Serum or Plasma**

**Reference Values:**

Reference Range: 10 – 100 ng/mL

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### AMPMX 62712

**Amphetamine-Type Stimulants Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamines). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy); 3,4-methylenedioxymethamphetamine (MDA); and 3,4-methylenedioxymethylamphetamine (MDEA). (1) Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease to synthesize. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDMA and MDEA are metabolized to MDA. (1) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. (2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves to the colon by the 16th week of gestation. (3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis. (2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters such as low-birth weight. (4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and...
abnormal sleep patterns. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of any 1 of the following: amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or 3,4-methylenedioxyethylamphetamine at >50 ng/g is indicative of in utero exposure up to 5 months before birth.

**Reference Values:**

<table>
<thead>
<tr>
<th></th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
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<tr>
<td>Positives</td>
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<td>Cutoff concentrations:</td>
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<tr>
<td>Methamphetamine by LC-MS/MS:</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>3,4-Methylenedioxyamphetamine by LC-MS/MS:</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>3,4-Methylenedioxymethamphetamine by LC-MS/MS:</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>3,4-Methylenedioxyethylamphetamine by LC-MS/MS:</td>
<td>50 ng/g</td>
</tr>
</tbody>
</table>

**Clinical References:**

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**AMPHM 84371**

**Amphetamine-Type Stimulants, Confirmation, Meconium**

**Clinical Information:** Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamine). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine (MDMA, Ecstasy); 3,4-methylenedioxymethamphetamine (MDA); and 3,4-methylenedioxyethylamphetamine (MDEA).(1) Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease to synthesize. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDA and MDEA are metabolized to MDA.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters such as low-birth weight.(4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns.(5)
**Useful For:** Detection of in utero drug exposure up to 5 months before birth

**Interpretation:** The presence of any 1 of the following: amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or 3,4-methylenedioxyethylamphetamine at >50 ng/g is indicative of in utero exposure up to 5 months before birth.

**Reference Values:**

Negative
Positives are reported with a quantitative LC-MS/MS result.

Cutoff concentrations:
- AMPHETAMINE BY LC-MS/MS
  - 50 ng/g
- METHAMPHETAMINE BY LC-MS/MS
  - 50 ng/g
- 3,4-METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS
  - 50 ng/g
- 3,4-METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS
  - 50 ng/g
- 3,4-METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS
  - 50 ng/g

**Clinical References:**

1. Disposition of Toxic Drugs and Chemical in Man. Edited by RC Baselt. Foster City, CA, Biochemical Publications, 2008 pp 83-86; 947-952; 993-999

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**FASCC**

**Amphetamines Analysis, Serum**

**Reference Values:**

Reference Range:
- Amphetamines: Cutoff: 50

Confirmation Threshold: 10 mg/mL

**AMPHX**

**Amphetamines Confirmation, Chain of Custody, Urine**

**Clinical Information:** Amphetamines are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Phentermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All of the other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of narcolepsy, attention-deficit disorder/attention-deficit hyperactivity disorder, and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this...
manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phentermine, methylenedioxyamphetamine (MDA: a metabolite of MDMA and MDEA), methylenedioxyxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA) Chain-of-custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of amphetamines in urine at concentrations >500 ng/mL is a strong indicator that the patient has used these drugs within the past 3 days. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegiline (metabolized to methamphetamine and amphetamine); and clobenzorex, famprofazone, fenethylline, fenproporex, and mfenorex, which are amphetamine pro-drugs.

**Reference Values:**

**Cutoff concentrations:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cutoff Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMUNOASSAY SCREEN</td>
<td>&lt;500 ng/mL</td>
</tr>
<tr>
<td>AMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>METHAMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>PHENTERMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>PSEUDOEPHEDRINE/EPHEDRINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL reported as negative</td>
</tr>
</tbody>
</table>

Useful For: Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phentermine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA).

Interpretation: The presence of amphetamines in urine at concentrations >500 ng/mL is a strong indicator that the patient has used these drugs within the past 3 days. Methylenedioxyamphetamine (MDA) is a metabolite of MDMA and MDEA. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegiline (metabolized to methamphetamine and amphetamine); and clobenzorex, famprofazole, fenethylline, fenproporex, and mefenorex, which are amphetamine pro-drugs.

Reference Values:
Negative

Cutoff concentrations:
AMPHEMATINE BY LC-MS/MS
<25 ng/mL

METHAMPHETAMINE BY LC-MS/MS
<25 ng/mL

PHENTERMINE BY LC-MS/MS
<25 ng/mL

METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS
<25 ng/mL

METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS
<25 ng/mL

PSEUDOEPHEDRINE/EPHEDRINE BY LC-MS/MS
<25 ng/mL reported as negative


Ampicillin, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Amylase, Body Fluid**

**Clinical Information:** Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes.

**Useful For:** Evaluation of patients suspected of having acute pancreatitis. If ascites are present, it is occasionally used to demonstrate pancreatic inflammation. If this is true, the level will be at least ten times that of serum.

**Interpretation:** No control range has been obtained so interpretation is qualitative and thought to be positive for pancreatitis if >1,100 U/L (10 times the serum normal range).

**Reference Values:**

Not applicable


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**Amylase, Isoenzymes**

**Reference Values:**

Pancreatic amylase
- 6-35 months: 2-28 U/L
- 3-6 years: 8-34 U/L
- 7-17 years: 9-39 U/L
- 18 years and older: 12-52 U/L

Salivary amylase
- 18 months and older: 9-86 U/L

Total amylase
**Amylase, Pancreatic Cyst**

**Clinical Information:** Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Measurement of amylase in pancreatic cyst fluid is often used in conjunction with tumor markers, carcinoembryonic antigen and CA19-9, as an aid in the differential diagnosis of pancreatic cysts lesions. Amylase seems to be particularly helpful in excluding pancreatic pseudocysts. A number of studies have demonstrated that amylase levels are typically very high, usually in the thousands in pseudocysts, therefore, low amylase values virtually excludes pseudocysts. Based on the evidence available, the American College of Gastroenterology (ACG) practice guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts suggest that an amylase cutoff value of 250 U/L is useful to exclude pseudocysts.

**Useful For:** Aids in distinguishing between pseudocysts and other types of pancreatic cysts, when used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers

**Interpretation:** A pancreatic cyst fluid amylase concentration of <250 U/L indicates a low risk of a pseudocyst and is more consistent with cystic neoplasms such as mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasm (IPMN), serous cystadenomas, cystic neuroendocrine tumor, and mucinous cystadenocarcinoma. High pancreatic cyst fluid amylase values are nonspecific and occur both in pseudocysts and some mucin-producing cystic neoplasms including MCN, IPMN, and mucinous cystadenocarcinoma. In-house studies to verify this cutoff value showed that 94% (66/70) of pseudocysts had a value of > or =250 U/L. Cysts with amylase levels of <250 U/L included 69% of adenocarcinomas, 31% of intraductal papillary mucinous neoplasia, 55% of mucinous cystadenomas, 64% serous cystadenomas, and 6% of pseudocysts. Therefore, using a cutoff of <250 U/L to exclude a pseudocyst has 94% sensitivity and 42% specificity.

**Reference Values:**
An interpretive report will be provided.


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**Amylase, Pancreatic, Body Fluid**

**Clinical Information:** Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Since the clinical use of amylase activity is usually to detect pancreatitis, the p-amylase form provides a useful test in the laboratory diagnosis of acute pancreatitis. Pleural effusion may occur secondary to inflammatory pancreatic disease. Exocrine products of the pancreas will occur in such body fluids.
Useful For: Pancreatic amylase will most frequently be ordered as a serum test to detect acute pancreatitis. If a pleural effusion occurs as a complication of acute pancreatitis, excessive amounts of pancreatic amylase (p-amylase) in the effusion points to pancreatitis as the cause.

Interpretation: Elevated pleural effusion alpha-amylase suggests acute pancreatitis as the cause of the effusion.

Reference Values: Not applicable


Amylase, Pancreatic, Serum

Clinical Information: Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Since the clinical use of amylase activity is usually to detect pancreatitis, the pancreatic amylase (p-amylase) form provides the single most useful test in the laboratory diagnosis of acute pancreatitis. Total serum amylase continues to be the most widely used clinical test for the diagnosis of acute pancreatitis. Its use has been justified on the basis of its accuracy of 95%. The problem with its use is that it has relatively low specificity of between 70% and 80%.

Useful For: Diagnosing acute pancreatitis

Interpretation: Pancreatic amylase is elevated in acute pancreatitis within 12 hours of onset and persists 3 to 4 days. The elevation is usually 4-fold to 6-fold the upper reference limit. Macroamylase may cause less dramatic and more persistent elevations of p-amylase over weeks or months. This is usually accompanied by a reduced amylase clearance. Values over the normal reference interval in patients with histories consistent with acute pancreatitis are confirmatory. Peak values are often 200 U/L or higher. Macroamylasemia may cause small, but persistent elevations of amylase. An elevation of total serum alpha-amylase does not specifically indicate a pancreatic disorder since the enzyme is produced by the salivary glands, mucosa of the small intestine, ovaries, placenta, liver, and the lining of the fallopian tubes. Two isoenzymes, pancreatic and salivary, are found in serum. Pancreatic amylase has been shown to be more useful than total amylase when evaluating patients with acute pancreatitis.

Reference Values:
0-<24 months: 0-20 U/L
2-<18 years: 9-35 U/L
> or =18 years: 11-54 U/L


Amylase, Random, Urine

Clinical Information: Amylases are enzymes that hydrolyze complex carbohydrates. They are produced by a number of organs and tissues, predominantly the exocrine pancreas (P-type amylase) and salivary glands (S-type amylase). Plasma amylases are of relatively low molecular weight for an enzyme (55,000 to 60,000 daltons) and enter the urine through glomerular filtration. Conditions that cause increased entry of amylase into plasma (eg, acute pancreatitis) will thus result in increased urinary excretion of amylase. Urinary amylase is therefore sometimes used in the diagnosis of acute pancreatitis. However, the rate of urinary amylase excretion appears to be less sensitive than plasma markers, and is not specific for the diagnosis of acute pancreatitis. Similar to other low molecular weight proteins filtered by glomeruli, amylases are reabsorbed to an extent by the proximal tubule. Thus, conditions associated with increased production and glomerular filtration of other low molecular weight proteins that compete
with tubular reabsorption of amylase, or conditions of proximal tubular injury may increase urinary amylase excretion. Also, a number of disorders other than acute pancreatitis may cause increases in plasma amylase concentrations and consequent increases in urinary amylase excretion. These conditions include burns, ketoacidosis, myeloma, light-chain proteinuria, march hemoglobinuria, acute appendicitis, intestinal perforation, and following extracorporeal circulation. Urinary amylase clearance is increased about 3-fold for 1 to 2 weeks in patients with acute pancreatitis. A value > 550 U/L has been reported as 62% sensitive and 97% specific for acute pancreatitis (3), while a value > 2000 U/L has been reported as 62% sensitive and 97% specific for acute pancreatitis (4). Quantitation of urinary amylase excretion is also useful in monitoring for rejection following pancreas transplantation. The duodenal cuffs of donor pancreases are often surgically anastomosed to the recipient's bladder at the time of pancreas transplantation, allowing for drainage of exocrine pancreas fluid into the bladder. In pancreatic rejection, urinary amylase excretion decreases. In patients with pancreas transplants that drain into the urinary system, a drop in urinary amylase of more than 25% from that patient’s baseline value can indicate acute rejection (5). In this situation, collecting a timed urine sample and expressing the urinary amylase level as Units excreted/hr might reduce variability and improve test performance (6).

**Useful For:** Assessment of acute rejection of bladder-drained pancreas transplants

**Diagnoses of acute pancreatitis**

**Interpretation:** Decreases in urinary amylase excretion of greater than 30% to 50%, relative to baseline values, may be associated with acute pancreas allograft rejection. Because there is large day-to-day variability in urinary amylase excretion following pancreas transplantation, if a significant decrease is noted, it should be confirmed by a second collection. There is also large inter-individual variability in urinary amylase excretion among pancreas transplant recipients. Acute rejection is usually not established solely by changes in urinary amylase excretion, but by tissue biopsy. Levels are elevated in acute pancreatitis (but with poor sensitivity and specificity).

**Reference Values:**

No established reference values

**Clinical References:**


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**Amylase, Timed Collection, Urine**

**Clinical Information:** Amylases are enzymes that hydrolyze complex carbohydrates. They are produced by a number of organs and tissues, predominantly the exocrine pancreas (P-type amylase) and salivary glands (S-type amylase). Plasma amylases are of relatively low molecular weight for an enzyme (55,000-60,000 daltons) and enter the urine through glomerular filtration. Conditions that cause increased entry of amylase into plasma (eg, acute pancreatitis) will thus result in increased urinary excretion of amylase. Therefore, urinary amylase is sometimes used in the diagnosis of acute pancreatitis. However, the rate of urinary amylase excretion appears to be less sensitive than plasma markers, and is not specific for the diagnosis of acute pancreatitis. Similar to other low-molecular-weight proteins filtered by glomeruli, amylases are reabsorbed to an extent by the proximal tubule. Thus, conditions associated with increased production and glomerular filtration of other low-molecular-weight proteins that compete with tubular reabsorption of amylase or conditions of proximal tubular injury may increase urinary amylase excretion. Also, a number of disorders other than acute pancreatitis may cause increases in plasma amylase concentrations and consequent increases in urinary amylase excretion. These conditions include burns, ketoacidosis, myeloma, light-chain proteinuria, march hemoglobinuria, acute appendicitis,
intestinal perforation, and following extracorporeal circulation. Quantitation of urinary amylase excretion is also useful in monitoring for rejection following pancreas transplantation. The duodenal cuffs of donor pancreases are often surgically anastomosed to the recipient's bladder at the time of pancreas transplantation, allowing for drainage of exocrine pancreas fluid into the bladder. In pancreatic rejection, urinary amylase excretion decreases.

**Useful For:** Assessment of acute rejection of bladder-drained pancreas transplants As an aid in the diagnosis of acute pancreatitis

**Interpretation:** Decreases in urinary amylase excretion of greater than 30% to 50%, relative to baseline values, may be associated with acute pancreas allograft rejection. Because there is large day-to-day variability in urinary amylase excretion following pancreas transplantation, if a significant decrease is noted, it should be confirmed by a second collection. There is also large inter-individual variability in urinary amylase excretion among pancreas transplant recipients. Collecting a timed urine specimen and expressing the urinary amylase level as Units excreted/hour might reduce variability and improve test performance. However, acute rejection is usually not established solely by changes in urinary amylase excretion, but by tissue biopsy. Urinary amylase is elevated in acute pancreatitis, but the test has poor sensitivity and specificity.

**Reference Values:**
3-26 U/hour

**Clinical References:**

**Amylase, Total, Serum**

**Clinical Information:** Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced primarily by the exocrine pancreas where the enzyme is synthesized by the acinar cells and then secreted into the intestinal tract by way of the pancreatic duct system. Amylases also are produced by the salivary glands, small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Pancreatic and salivary isoenzymes are found in serum.

**Useful For:** Diagnosis and management of pancreatitis Evaluation of pancreatic function

**Interpretation:** In acute pancreatitis, a transient rise in serum amylase activity occurs within 2 to 12 hours of onset; levels return to normal by the third or fourth day. A 4- to 6-fold elevation of amylase activity above the reference limit is usual with the maximal levels obtained in 12 to 72 hours. However, a significant number of subjects show lesser elevations and sometimes none. The magnitude of the elevation of serum enzyme activity is not related to the severity of pancreatic involvement. Normalization is not necessarily a sign of resolution. In acute pancreatitis associated with hyperlipidemia, serum amylase activity may be spuriously normal; the amylasemia may be unmasked either by serial dilution of the serum or ultracentrifugation. A significant amount of serum amylase is excreted in the urine, and therefore, elevation of serum activity is reflected in the rise of urinary amylase activity. Urine amylase, as compared to serum amylase, appears to be more frequently elevated, reaches higher levels and persists for longer periods. However, the receiver operator curves (ROC) of various serum and urine amylase assays demonstrated that all urine assays had poorer diagnostic utility than all serum assays. In quiescent chronic pancreatitis, both serum and urine activities are usually subnormal. Because it is produced by several organs, amylase is not a specific indicator of pancreatic function. Elevated levels also may be seen in a number of nonpancreatic disease processes including mumps, salivary duct obstruction, ectopic pregnancy, and intestinal obstruction/infarction.

**Reference Values:**
0-30 days: 0-6 U/L
31-182 days: 1-17 U/L  
183-365 days: 6-44 U/L  
1-3 years: 8-79 U/L  
4-17 years: 21-110 U/L  
> or =18 years: 26-102 U/L  


FABP 91408  

Amyloid Beta-Protein  
Reference Values:  
Adult Reference Range(s):  
20-80 pg/ml  

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.  

82091  

Amyloid Protein Identification, Paraffin, LC-MS/MS  
Clinical Information: Amyloidosis is a group of hereditary and acquired diseases that are unified by extracellular tissue deposition of misfolded proteins resulting in end organ damage. Amyloidosis can be a systemic or localized disease. Although many cases of amyloidosis are hereditary, most are acquired as the result of an underlying monoclonal B-cell/plasma cell malignancy, as a phenomenon of aging, or as the result of long-standing chronic inflammation. Specific amyloid-related diseases are therefore associated with specific amyloid proteins. These include kappa or lambda immunoglobulin light chains (AL amyloid), transthyretin (ATTR amyloid), serum amyloid A (SAA amyloid), and other uncommon subtypes. Because treatment of amyloidosis patients differs radically for the different amyloid subtypes, it is critically important to accurately identify the proteins that constitute the amyloid deposits. The basic diagnosis of amyloidosis is typically achieved by Congo red staining of paraffin-embedded tissue biopsy specimens obtained from diverse anatomic sites and demonstrating Congo red-positive, apple-green birefringent, amyloid deposits in the tissues. The next step is to definitively subtype the amyloid deposits. This test fulfills that need. It relies on laser microdissection of Congo red-positive amyloid deposits followed by analysis by liquid chromatography-tandem mass spectrometry to accurately determine the identity of the proteins that constitute the amyloid.  

Useful For: Definitive identification of amyloid proteins  
Interpretation: An interpretation will be provided.  
Amyloidosis, Transthyretin-Associated Familial, Reflex, Blood

Clinical Information: The systemic amyloidoses are a group of diseases that result from the abnormal deposition of amyloid in various tissues of the body. They have been classified into 3 major types: primary, secondary, and hereditary. The most common form of amyloidosis (AL) is a disease of the bone marrow called primary systemic AL (immunoglobulin light chain). Secondary AL usually occurs in tandem with chronic infectious or inflammatory diseases, such as rheumatoid arthritis, tuberculosis, or osteomyelitis. Familial or hereditary AL is the least common form. Determining the specific type of AL is imperative in order to provide both an accurate prognosis and appropriate therapies. Familial or hereditary transthyretin AL is an autosomal dominant disorder caused by mutations in the transthyretin gene (TTR). The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic transthyretin (TTR) protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. TTR-associated AL is progressive over a course of 5 to 15 years and usually ends in death from cardiac or renal failure or malnutrition. Affected individuals may present with a variety of symptoms including peripheral neuropathy, blindness, cardiomyopathy, nephropathy, autonomic nervous dysfunction, and bowel dysfunction. More than 90 mutations that cause TTR-associated familial AL have now been identified within the TTR gene. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of AL. Mayo Medical Laboratories recommends a testing strategy that includes both protein analysis by mass spectrometry (MS) and TTR gene analysis by DNA sequencing (ATTRZ / TTR Gene, Full Gene Analysis) for patients in whom TTR-associated familial AL is suspected. The structure of TTR protein in plasma is first determined by MS. Only the transthyretin (also known as prealbumin) is analyzed for amino acid substitutions. Other proteins involved in other less common forms of familial amyloidosis are not examined. If no alterations are detected, gene analysis will not be performed unless requested by the provider (ie, when the diagnosis is still strongly suspected; to rule out the possibility of a false negative by MS). In all cases demonstrating a structural change by MS, the entire TTR gene will be analyzed by DNA sequence analysis to identify and characterize the observed alteration (gene mutation or benign polymorphism). For predictive testing in cases where a familial mutation is known, testing for the specific mutation by DNA sequence analysis (FMTT / Familial Mutation, Targeted Testing) is recommended. These assays do not detect mutations associated with non-TTR forms of familial AL. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

Useful For: Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

Interpretation: The presence of a structural change in transthyretin (TTR) is suggestive of a gene mutation that requires confirmation by DNA sequence analysis. A negative result by mass spectrometry does not rule-out a TTR mutation. Mass spectrometric (MS) results are falsely negative if the amino acid substitution does not produce a measurable mass shift for the mutation transthyretin. Approximately 90% of the TTR mutations are positive by MS (see Cautions). After identification of the mutation at the DNA level, predictive testing for at-risk family members can be performed by molecular analysis (FMTT / Familial Mutation, Targeted Testing).

Reference Values: An interpretive report will be provided.

**Anaplasma phagocytophilum (Human Granulocytic Ehrlichiosis) Antibody, Serum**

**Clinical Information:** Human granulocyte ehrlichiosis (HGE) is a zoonotic infection caused by a rickettsia-like agent. The infection is acquired by contact with *Ixodes* ticks carrying the HGE agent. The deer mouse is the animal reservoir and, overall, the epidemiology is very much like that of Lyme disease and babesiosis. HGE is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. Since its first description in 1994, there have been approximately 50 cases of HGE described in the upper Midwest. The cellular target in HGE cases is the neutrophil. The organisms exist in membrane-lined vacuoles within the cytoplasm of infected host cells. Ehrlichial inclusions, called morulae, contain variable numbers of organisms. Single organisms, wrapped in vacuolar membranes have also been observed in the cytoplasm. Ehrlichia species occur in small electron-dense and large electron-lucent forms, but a clear life cycle has not been elucidated. Diagnosis of human ehrlichiosis has been difficult because the patient's clinical course is often mild and nonspecific, including fever, myalgias, arthralgias, and nausea. This is easily confused with other illnesses such as influenza or other tickborne zoonoses such as Lyme disease, babesiosis, and Rocky Mountain spotted fever. Clues to the diagnosis of ehrlichiosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated serum aminotransferase levels. However, these findings may also be present in patients with Lyme disease or babesiosis.

**Useful For:** As an adjunct in the diagnosis of human granulocytic ehrlichiosis

**Interpretation:** A positive result of an immunofluorescence assay (IFA) test (titer ≥ 1:64) suggests current or previous infection with human granulocytic ehrlichiosis. In general, the higher the titer, the more likely it is that the patient has an active infection. Seroconversion may also be demonstrated by a significant increase in IFA titers. During the acute phase of the infection, serologic tests are often nonreactive, PCR testing is available to aid in the diagnosis of these cases (see EHRL / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood).

**Reference Values:**

<1:64

illness that often resembles Rocky Mountain Spotted Fever.

**Reference Values:**
- IgG <1:64
- IgM <1:20

Anaplasma phagocytophilum is the tick-borne agent causing Human Granulocytic Ehrlichiosis (HGE). HGE is distinct and separate from Human Monocytic Ehrlichiosis (HME), caused by Ehrlichia chaffeensis. Serologic crossreactivity between A. phagocytophilum and E. chaffeensis is minimal (5-15%).

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**Anatomic Pathology Consultation, Wet Tissue**

**Clinical Information:** Mayo Clinic Rochester is staffed by pathologists whose expertise and special interests cover the entirety of pathology from surgical pathology with all of its respective subspecialty areas, to Hematopathology, Renal Pathology, and Dermatopathology. We provide consultation services on difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and sometimes transferred between the pathologists, as deemed appropriate for the type of case/diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Stained slides and paraffin blocks received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report/letter. If additional special stains/studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (e.g., cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. It is our goal to provide the highest possible level of diagnostic consultative service, while trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

**Useful For:** Obtaining a rapid, expert opinion on unprocessed specimens referred by the pathologist

**Interpretation:** Results of the consultation are reported in a formal pathology report which includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call. The formal pathology report is faxed. In our consultative practice, we strive to bring the customer the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

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**Anchovy, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.

associated with early puberty, or with any reduction in final height, or overt androgenization, and is generally regarded as a benign condition not requiring intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Elevated androstenedione levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild symptoms of estrogen excess, such as gynecomastia. Most mild-to-moderate elevations in androstenedione are idiopathic. However, pronounced elevations of androstenedione may be indicative of androgen-producing adrenal or gonadal tumors. In children, adrenal and gonadal tumors are uncommon, but many forms of congenital adrenal hyperplasia can increase serum androstenedione concentrations. Diagnosis always requires measurement of other androgen precursors (eg, OHPG, 17-alpha-hydroxypregnenolone, and DHEA-S) and cortisol, in addition to androstenedione. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex-steroids). An initial workup in adults might also include total and bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) and other androgenic steroids (eg, dehydroepiandrosterone sulfate [DHEA-S]). Diagnosis of congenital adrenal hyperplasia (CAH), in conjunction with measurement of other androgenic precursors, particularly, 17-alpha-hydroxyprogesterone (OHPG) (OHPG / 17-Hydroxyprogesterone, Serum), 17 alpha-hydroxypregnenolone, DHEA-S (DHEA-S / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), and cortisol (CORT / Cortisol, Serum). Monitoring CAH treatment, in conjunction with testosterone (TTST / Testosterone, Total, Serum), OHPG (OHPG / 17-Hydroxyprogesterone, Serum), and DHEA (DHEA_ / Dehydroepiandrosterone [DHEA], Serum). Diagnosis of premature adrenarche, in conjunction with gonadotropins (FSH / Follicle-Stimulating Hormone [FSH], Serum; LH / Luteinizing Hormone [LH], Serum) and other adrenal and gonadal sex-steroids and their precursors (TTBS / Testosterone, Total and Bioavailable, Serum or TGRP / Testosterone, Total and Free, Serum; EEST / Estradiol, Serum; DHES / Dehydroepiandrosterone Sulfate [DHEA-S], Serum; DHEA_ / Dehydroepiandrosterone [DHEA], Serum; SHBG / Sex Hormone Binding Globulin [SHBG], Serum; OHPG / 17-Hydroxyprogesterone, Serum).

**Interpretation:** Elevated androstenedione levels indicate increased adrenal or gonadal androgen production. Mild elevations in adults are usually idiopathic, or related to conditions such as polycystic ovarian syndrome (PCOS) in women, or use of androstenedione supplements in men and women. However, levels greater than or equal to 500 ng/dL can suggest the presence of an androgen-secreting adrenal, or less commonly, a gonadal, tumor. Androstenedione levels are elevated in more than 90% of patients with benign androgen-producing adrenal tumors, usually well above 500 ng/dL. Most androgen-secreting adrenal carcinomas also exhibit elevated androstenedione levels, but more typically show relatively larger elevations in 17-alpha-hydroxyprogesterone (OHPG) and dehydroepiandrosterone sulfate (DHEA-S) than in androstenedione, as they have often lost the ability to produce downstream androgens. Most androgen-secreting gonadal tumors also overproduce androstenedione, but often to lesser degrees than adrenal tumors. They also overproduce testosterone. In men and in women with high baseline androgen levels (eg, PCOS), the respective elevations of androstenedione and testosterone may not be high enough to allow unequivocal diagnosis of androgen-producing gonadal tumors. In these cases, an elevation of the usual ratio of testosterone to androstenedione of 1, to a ratio of >1.5, is a strong indicator of neoplastic androgen production. Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) mutations the most common cause of CAH (>90% of cases), usually have very high levels of androstenedione, often 5- to 10-fold elevations. OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extend as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common, 3 beta HSD-2 deficiency is characterized by low cortisol and substantial elevations in DHEA-S and 17-alpha-hydroxypregnenolone, while androstenedione is either low, normal, or, rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare STAR (steroidogenic acute regulatory protein) deficiency, all steroid hormone levels are low and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other
androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and their precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used for treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable. Girls below the age of 7 to 8 and boys before age 8 to 9 who present with early development of pubic hair or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty, or both. Measurement of DHEA-S, DHEA, and androstenedione, alongside determination of sensitive estradiol, total and bioavailable or free testosterone, sex hormone binding globulin (SHBG), and luteinizing hormone/follicle-stimulating hormone levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, and to a lesser degree, androstenedione, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. See Steroid Pathways in Special Instructions.

Reference Values:

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (Years)</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (prepubertal)</td>
<td>9.8-14.5</td>
<td>31-65</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.7-15.4</td>
<td>50-100</td>
</tr>
<tr>
<td>Stage III</td>
<td>11.8-16.2</td>
<td>48-140</td>
</tr>
<tr>
<td>Stage IV</td>
<td>12.8-17.3</td>
<td>65-210 Females*</td>
</tr>
<tr>
<td>Stage V</td>
<td>9.2-13.7</td>
<td>42-100</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.0-14.4</td>
<td>80-190</td>
</tr>
<tr>
<td>Stage III</td>
<td>10.7-15.6</td>
<td>77-225</td>
</tr>
</tbody>
</table>


Angiosarcoma, MYC (8q24) Amplification, FISH, Tissue

Clinical Information: Postradiation cutaneous angiosarcoma is a malignancy associated with very poor outcome and is consequently treated aggressively. Conversely, atypical vascular lesions are also
associated with radiation therapy, but are considered to be benign and do not require aggressive management. Therefore, the differentiation of these neoplasms is of considerable clinical importance. Postradiation cutaneous angiosarcomas are characterized by high-level amplification of MYC, whereas reactive and benign vascular lesions do not show amplification of MYC. Similar diagnostic difficulties arise in the setting of primary cutaneous vascular lesions. A subset of primary cutaneous angiosarcomas also shows high-level MYC amplification, which can be useful in the differentiation from benign primary cutaneous vascular lesions.

**Useful For:** Identifying MYC amplification to aid in the differentiation of cutaneous angiosarcomas from atypical vascular lesions after radiotherapy An aid in the diagnosis of primary cutaneous angiosarcoma

**Interpretation:** The MYC locus is reported as amplified when the MYC:D8Z2 ratio of 2.0 or greater and demonstrates 6 or more copies of the MYC locus. A lesion with a MYC:D8Z2 ratio <2.0 or showing a ratio of 2.0 or greater with less than 6 copies of MYC is considered to lack amplification of the MYC locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FACEC**

**Angiotensin Converting Enzyme, CSF**

**Reference Values:**
0.0 – 2.5 U/L

**ACE**

**Angiotensin Converting Enzyme, Serum**

**Clinical Information:** Angiotensin converting enzyme (ACE) participates in the renin cascade in response to hypovolemia. Its peptidase action on the decapetide angiotensinogen I results in the hydrolysis of a terminal histidyl leucine dipeptide and the formation of the octapeptide angiotensin II, a potent vasoconstrictor that increases blood pressure. The primary source of ACE is the endothelium of the lung. ACE activity is increased in sarcoidosis, a systemic granulomatous disease that commonly affects the lungs. In sarcoidosis, ACE is thought to be produced by epithelioid cells and macrophages of the granuloma. Currently, it appears that ACE activity reflects the severity of sarcoidosis: 68% positivity in those with stage I sarcoidosis, 86% in stage II sarcoidosis, and 91% in stage III sarcoidosis. Serum ACE also appears to reflect the activity of the disease; there is a dramatic decrease in enzyme activity in some patients receiving prednisone. Other conditions such as Gaucher disease, leprosy, untreated hyperthyroidism, psoriasis, premature infants with respiratory distress syndrome, adults with amyloidosis, and histoplasmosis have been associated with increased levels of ACE.

**Useful For:** Evaluation of patients with suspected sarcoidosis

**Interpretation:** An elevation in the level of serum angiotensin converting enzyme (ACE), along with radiographic evidence of infiltrates or adenopathy and organ biopsies showing noncaseating epithelial granulomas is suggestive of a diagnosis of sarcoidosis. Serum ACE is significantly higher in most (approximately 80%) patients with active sarcoidosis. ACE is also elevated in a number of other diseases and in approximately 5% of the normal adult population.

**Reference Values:**
> or =18 years: 8-53 U/L

The reference interval for pediatric patients may be up to 50% higher than that of adults.
**Clinical References:**
3. Personal observations from a Mayo pediatric normal range study using a manual method (Hana)

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**Angiotensin I, Plasma**

**Clinical Information:**
Angiotensin I is a ten amino acid peptide formed by Renin cleavage of Angiotensinogen (Renin Substrate). Angiotensin I has little biological activity except that high levels can stimulate Catecholamine production. It is metabolized to its biologically active byproduct Angiotensin II by Angiotensin Converting Enzyme (ACE). The formation of Angiotensin I is controlled by negative feedback of Angiotensin II and II on Renin release and by Aldosterone concentration. Levels of Angiotensin I are increased in many types of hypertension. Angiotensin I levels are used to determine Renin activity. Angiotensin I is excreted directly into the urine.

**Reference Values:**
Up to 25 pg/mL

This test was performed using a kit that has not been cleared or approved by the FDA and is designated as research use only. The analytic performance characteristics of this test have been determined by Inter Science Institute. This test is not intended for diagnosis or patient management decisions without confirmation by other medically established means.

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**Angiotensin II, Plasma**

**Clinical Information:**
Angiotensin II is an eight amino acid peptide formed by Angiotensin Converting Enzyme (ACE) cleavage of Angiotensin I. Angiotensin II is metabolized further to Angiotensin III. Angiotensin II release is controlled by Renin, blood pressure, blood volume, sodium balance and by Aldosterone concentration. Levels of Angiotensin II are increased in many types of hypertension. Angiotensin II stimulates the release of Anti-Diuretic Hormone, ACTH, Prolactin, Luteinizing Hormone, Oxytocin and Aldosterone. Angiotensin II increases vasoconstriction and inhibits tubular resorption of sodium, and can increase endothelial cell growth.

**Reference Values:**
10 - 60 pg/mL

This test was performed using a kit that has not been cleared or approved by the FDA and is designated as research use only. The analytic performance characteristics of this test have been determined by Inter Science Institute. This test is not intended for diagnosis or patient management decisions without confirmation by other medically established means.

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**Anisakis, Parasite, IgE**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**ANSE 82487**

**Anise, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:


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**FANSE 57520**

**Anatto Seed (Bixa orellana) IgE**

**Interpretation:**

<table>
<thead>
<tr>
<th>Class IgE (kU/L)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt;0.35 kU/L</td>
<td>Below Detection</td>
</tr>
<tr>
<td>0.35 - 0.69</td>
<td>Low Positive</td>
</tr>
<tr>
<td>0.70 - 3.49</td>
<td>Moderate Positive</td>
</tr>
<tr>
<td>3.50 - 17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>17.50 - 49.99</td>
<td>Strong Positive</td>
</tr>
<tr>
<td>50.00 - 99.99</td>
<td>Very Strong Positive</td>
</tr>
<tr>
<td>&gt;99.99</td>
<td>Very Strong Positive</td>
</tr>
</tbody>
</table>

### Reference Values:

<0.35 kU/L

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**FARHC 57648**

**Anti - Retinal Antibodies (CAR, MAR, Autoimmune Retinopathy), IHC**

**Reference Values:**

A final report will be attached in MayoAccess.

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**ADNAS 80204**

**Anti-DNase B Titer, Serum**

**Clinical Information:**

A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

**Useful For:** Demonstration of acute or recent streptococcal infection

**Interpretation:** Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of
individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolyisin O. For such patients, performance of an alternative streptococcal antibody test such as anti-DNase B is recommended.

**Reference Values:**

<5 years: < or =250 U/mL  
5-17 years < or =375 U/mL  
> or =18 years: < or =300 U/mL


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**FAEAB 91854**

**Anti-Enterocyte Antibodies**

**Reference Values:**

- IgG: Negative
- IgA: Negative
- IgM: Negative

**FAHMG 75157**

**Anti-HMGCR Autoantibodies**

**Clinical Information:** HMGCR Abs (3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase) are associated with necrotizing myopathy that is commonly related to statin exposure.

**Interpretation:** Anti-HMGCR antibodies are usually found in association with necrotizing myopathy related to statin therapy. However, about 30% of Anti-HMGCR positive patients with necrotizing myopathy have never been exposed to statins. The literature suggests that false positives are extremely rare. As a lab developed test (LDT), approval or clearance by the FDA is not required. This test may be used for clinical purposes and should not be regarded as investigational or for research. Diagnosis Number (%) Pos Polymyositis/Dermatomyositis 2/76(2.6)  
Primary Sjogren's Syndrome 0/30(0.0)  
Rheumatoid Arthritis 0/30(0.0)  
Systemic Sclerosis 0/30(0.0)  
Normal Controls 0/47(0.0)

**Reference Values:**

- Negative: <20  
- Weak Positive: 20 â€“ 39  
- Moderate Positive: 40 â€“ 59  
- Strong Positive: >=60

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**FIGA 57552**

**Anti-IgA**

**Reference Values:**

<99 U/mL

Patients with IgG antibodies against IgA may suffer from anaphylactoid reactions when given IVIG that contains small quantities of IgA. In one study (Clinical Immunology 2007; 122:156) five out of eight patients with IgG anti-IgA antibodies developed anaphylactoid reactions when IVIG was administered.

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**FANTI 57892**

**Anti-IgE**

**Reference Values:**
Normal

This ELISA measures IgG antibodies specific for IgE. A result of normal indicates that the level of IgG anti-IgE antibodies is similar to that seen in a population of healthy individuals. A result of elevated indicates an increased level of IgG anti-IgE antibodies compared to healthy individuals. These autoantibodies have been implicated as a causative agent in autoimmune chronic urticaria and atopic dermatitis.

**FAIRA 75054**

**Anti-IgE Receptor Antibody**

**Interpretation:** Chronic autoimmune urticaria (CIU) may be associated with autoantibodies to the high affinity IgE receptor (Fc-epsilon R1) or to IgE. In the presence of the autoantibodies, cross-linking of the Fc-epsilon-R1 receptor occurs, leading to basophil activation. The laboratory tests for the activation of donor basophils by CIU serum by analyzing the expression of the basophil specific ectoenzyme, CD203c. CD203c is upregulated on the surface of basophils following activation. A positive result is indicative of the presence of autoantibodies associated with CIU, but may also be due to other basophil-activating serum factors. Results must be correlated with clinical findings. The reference range was developed by the National Jewish Health Advanced Diagnostic Laboratories (unpublished data).

**Reference Values:**

<13 % of basophils


**FANBF 57173**

**Anti-Nuclear Ab (FANA), Body Fluid**

**Reference Values:**

ANA Titer: <1:10
ANA Pattern: No Pattern

**FCLNE 91321**

**Anti-Phosphatidylcholine Ab**

**Reference Values:**

Anti-Phosphatidylcholine IgA: <12.0 U/mL

Anti-Phosphatidylcholine IgG: <12.0 U/mL

Anti-Phosphatidylcholine IgM: <12.0 U/mL

Reference Range applies to Antiphosphatidylcholine IgA, IgG & IgM:

<table>
<thead>
<tr>
<th>Normal</th>
<th>&lt;12.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivocal</td>
<td>12.0 – 18.0</td>
</tr>
<tr>
<td>Elevated</td>
<td>&gt;18.0</td>
</tr>
</tbody>
</table>

**FPHET 91322**

**Anti-Phosphatidylethanolamine Panel**

**Reference Values:**

Anti-Phosphatidylethanolamine IgA
<12.0 U/mL

Anti-Phosphatidylethanolamine IgG
<12.0 U/mL
Anti-Phosphatidylethanolamine IgM
<12.0 U/mL

Reference Range applies to Antiphosphatidylethanolamine IgA, IgG, & IgM
Normal: <12.0
Equivocal: 12.0 â€“ 18.0
Elevated: >18.0

FARWB
57647

Anti-Retinal Antibodies (CAR, MAR, Autoimmune Retinopathy), Western Blot

Reference Values:
A final report will be attached in MayoAccess.

ABID2
8988

Antibody Identification, Erythrocytes

Clinical Information: After exposure to foreign red blood cells via transfusion or pregnancy, some people form antibodies which are capable of the destruction of transfused red cells or of fetal red cells in utero. It is important to identify the antibody specificity in order to assess the antibody’s capability of causing clinical harm and, if necessary, to avoid the antigen on transfused red blood cells.

Useful For: Assessing positive pretransfusion antibody screens, transfusion reactions, hemolytic disease of the newborn, and autoimmune hemolytic anemias

Interpretation: Specificity of alloantibodies will be stated. The patient’s red blood cells will be typed for absence of the corresponding antigen(s) or as an aid to identification in complex cases. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

Reference Values:
Negative
If positive, antibodies will be identified and corresponding special red cell antigen typing on patient's red blood cells will be performed. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.


ABSCM
8956

Antibody Screen, Erythrocytes

Clinical Information: Transfusion and pregnancy are the primary means of sensitization to red cell antigens. In a given population, 2% to 4% of the general population possess irregular red cell alloantibodies. Such antibodies may cause hemolytic disease of the newborn or hemolysis of transfused donor red blood cells. Autoantibodies react against the patient's own red cells as well as the majority of cells tested. Autoantibodies can be clinically benign or can hemolyze the patient's own red blood cells, such as in cold agglutinin disease or autoimmune hemolytic anemia.

Useful For: Detection of allo- or autoantibodies directed against red blood cell antigens in the settings of pretransfusion testing Evaluation of transfusion reactions Evaluation of hemolytic anemia

Interpretation: A positive result (antibody detected) necessitates antibody identification to establish the specificity and clinical significance of the antibody detected. Negative â€“ no antibody detected.

Reference Values:
Negative
If positive, antibody identification will be performed.

Antibody Titer, Erythrocytes

Clinical Information: Some maternal IgG alloantibodies to red blood cell antigens will cross the placenta and cause hemolysis of antigen-positive fetal red cells. The resulting fetal anemia and hyperbilirubinemia can be harmful or even fatal to the fetus or the newborn.

Useful For: Monitoring antibody levels during pregnancy to help assess the risk of hemolytic disease of the newborn.

Interpretation: The specificity of the maternal alloantibody will be stated. The titer result is the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed. If the antibody problem identified is not relevant in hemolytic disease of the newborn or if titrations are not helpful, the titer will be canceled and will be replaced by ABID2 / Antibody Identification, Erythrocytes. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

Reference Values:
Negative
If positive, result will be reported as the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed.


Antibody to Extractable Nuclear Antigen Evaluation, Serum

Clinical Information: See individual unit codes.

Useful For: See individual unit codes.

Interpretation: See individual unit codes.

Reference Values:
SS-A/Ro ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

SS-B/La ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Sm ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

RNP ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Scl 70 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.
Jo 1 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: See individual unit codes.

FADDS
57772
Antidepressant Drug Screen, Qualitative
Reference Values:
Antidepressant screen includes the analysis for:
Amytriptyline, Clomipramine and Desmethylclomipramine, Cyclobenzaprine, Desipramine, Doxepin and Desmethyldoxepin, Fluoxetine and Norfluoxetine, Imipramine, Maprotiline, Nortriptyline, Paroxetine, Protriptyline, Sertraline and Desmethylsertraline, Trimipramine.

FASQN
57740
Antidepressant Drug Screen, Ur, Quantitative
Reference Values:
Antidepressant screen includes the analysis for: amitriptyline, clomipramine and desmethylclomipramine, cyclobenzaprine, desipramine, doxepin and desmethyldoxepin, fluoxetine and norfluoxetine, imipramine, maprotiline, nortriptyline, paroxetine, protriptyline, sertraline and desmethylsertraline, trimipramine.

MMLYP
81602
Antimicrobial Susceptibility Panel, Yeast
Clinical Information: Candida species are the fourth leading cause of nosocomial infections and are also frequent causes of community-acquired infections. Antifungal susceptibility testing may aid in the management of patients with invasive infections due to Candida species or patients who appear to be experiencing therapeutic failure. The Clinical Laboratory Standards Institute has approved the use of a broth microdilution method for determining the susceptibility of Candida species.

Useful For: Determining in vitro quantitative antifungal susceptibility (minimum inhibitory concentration) of non-fastidious yeast Testing may be warranted to aid in the management of certain circumstances, such as: -Refractory oropharyngeal infections due to Candida species in patients who appear to be experiencing therapeutic failure with standard agents at standard doses -Invasive infections due to Candida species when the utility of azole antifungal agents is uncertain (eg, when the infection is due to a non-Candida albicans organism)

Interpretation: The minimum inhibitory concentration (MIC) is recorded as the lowest concentration of antifungal agent producing complete inhibition of growth. Interpretive breakpoints are available for Candida albicans, Candida glabrata, Candida guilliermondii, Candida krusei, Candida parapsilosis, and Candida tropicalis for limited drugs (see tables below); the clinical relevance of testing any other organism-drug combination remains uncertain. Agent MIC Ranges on Yeast Plate (mcg/mL) Candida albicans Interpretations (mcg/mL) Susceptible Dose Dependent Intermediate Resistant Amphotericin 0.12-8 - - - - Anidulafungin 0.015-8 < or =0.25 - 0.5 > or =1 Fluconazole 0.125-256 < or =2 4 - > or =8 Itraconazole 0.015-16 - - - - Micafungin 0.008-8 < or =0.25 - 0.5 > or =15-Flucytosine 0.06-64 - - - - Voriconazole 0.008-8 < or =0.12 0.25-0.5 - > or =1 Caspofungin 0.008-8 < or =0.25 - 0.5 > or =1 Posaconazole 0.008-8 - - - - Agent MIC Ranges on Yeast Plate (mcg/mL) Candida glabrata Interpretations (mcg/mL) Susceptible Dose Dependent Intermediate Resistant Amphotericin 0.12-8 - - - - Anidulafungin 0.015-8 < or =0.12 - 0.25 > or =0.5 Fluconazole 0.125-256 - < or =32 - > or =64 Itraconazole 0.015-16 - - - - Micafungin 0.008-8 < or =0.06 - 0.12 > or =0.25 5-Flucytosine 0.06-64 - - - - Voriconazole 0.008-8 - - - - Caspofungin 0.008-8 < or =0.12 - 0.25 > or =1 Posaconazole 0.008-8 - - - - Agent MIC Ranges on Yeast Plate (mcg/mL) Candida guilliermondii Interpretations (mcg/mL) Susceptible Dose Dependent Intermediate Resistant Amphotericin 0.12-8 - - - - Anidulafungin 0.015-8 < or =2 - 4 > or =8 Fluconazole 0.125-256 - - - - Itraconazole 0.015-16 - - - - Micafungin 0.008-8 < or =2 - 4 > or =8 5-Flucytosine 0.06-64 - - - - Voriconazole 0.008-8 - - - - Caspofungin 0.008-8 < or =2
- 4 or =8 Posaconazole 0.008-8 - - - - Agent MIC Ranges on Yeast Plate (mcg/mL) Candida krusei
Interpretations (mcg/mL) Susceptible Dose Dependent Susceptible Intermediate Resistant Amphotericin 0.12-8 - - - - Anidulafungin 0.015-8 < or =0.25 - 0.5 > or =1 Itraconazole 0.015-16 - - - - Micafungin 0.008-8 < or =0.25 - 0.5 > or =1 5-Flucytosine 0.06-64 - - - - Voriconazole 0.008-8 < or =0.5 1 - > or =2 Caspofungin 0.008-8 < or =0.25 - 0.5 > or =1 Posaconazole 0.008-8 - - - - Agent MIC Ranges on Yeast Plate (mcg/mL) Candida parapsilosis Interpretations (mcg/mL) Susceptible Dose Dependent Susceptible Intermediate Resistant Amphotericin 0.12-8 - - - - Anidulafungin 0.015-8 < or =2 - 4 > or =8 Fluconazole 0.125-256 < or =2 4 - > or =8 Itraconazole 0.015-16 - - - - Micafungin 0.008-8 < or =2 - 4 > or =8 5-Flucytosine 0.06-64 - - - - Voriconazole 0.008-8 < or =0.12 0.25-0.5 - > or =1 Caspofungin 0.008-8 < or =2 - 4 > or =8 Posaconazole 0.008-8 - - - - Agent MIC Ranges on Yeast Plate (mcg/mL) Candida tropicalis Interpretations (mcg/mL) Susceptible Dose Dependent Susceptible Intermediate Resistant Amphotericin 0.12-8 - - - - Anidulafungin 0.015-8 < or =0.25 - 0.5 > or =1 Fluconazole 0.125-256 < or =2 4 - > or =8 Itraconazole 0.015-16 - - - - Micafungin 0.008-8 < or =0.25 - 0.5 > or =1 5-Flucytosine 0.06-64 - - - - Voriconazole 0.008-8 < or =0.12 0.25-0.5 - > or =1 Caspofungin 0.008-8 < or =0.25 - 0.5 > or =1 Posaconazole 0.008-8 - - - - Please note that Candida krusei is intrinsically resistant to fluconazole regardless of in vitro MIC result.

Reference Values:
Results reported in mcg/mL


MMLRG 81601

Antimicrobial Susceptibility, Acid-Fast Bacilli, Rapidly Growing

Clinical Information: The rapidly growing species of mycobacteria (eg, Mycobacterium fortuitum, Mycobacterium peregrinum, Mycobacterium chelonae, Mycobacterium abscessus, and Mycobacterium mucogenicum) are seen with increasing frequency as causes of infection. Some examples of infections caused by this group of mycobacteria are empyema, subcutaneous abscess, cutaneous ulcerative and nodular lesions, peritonitis, endometriosis, bacteremia, keratitis, and urinary tract, prosthetic joint, wound, and disseminated infections. Rapidly growing mycobacteria differ from other species of mycobacteria by their growth rates, metabolic properties, and antimicrobial susceptibility profiles. Most species are susceptible to some of the traditional antimycobacterial agents, but rapidly growing species may exhibit resistance to certain antimycobacterial agents. In contrast, they are often susceptible to several of the antibacterial agents used to treat common bacterial infections. Therefore, the antimicrobial susceptibility profile of an organism within this group varies depending on the species. Antimicrobials tested in this assay are amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, imipenem, tobramycin, trimethoprim/sulfamethoxazole, linezolid, moxifloxacin, minocycline and tigecycline.

Useful For: Determination of resistance of rapidly growing mycobacteria to antimicrobial agents

Interpretation: Results are reported as the minimum inhibitory concentration in micrograms/mL.

Reference Values:

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Susceptible (mcg/mL)</th>
<th>Intermediate (mcg/mL)</th>
<th>Resistant (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt; or =16</td>
<td>32</td>
<td>&gt; or =64</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>&lt; or =16</td>
<td>32-64</td>
<td>&gt; or =128</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =1.0</td>
<td>2.0</td>
<td>&gt; or =4.0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =2.0</td>
<td>4.0</td>
<td>&gt; or =8.0</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>&lt; or =1.0</td>
<td>2.0-8.0</td>
<td>&gt; or =16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&lt; or =4.0</td>
<td>8.0</td>
<td>&gt; or =16</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&lt; or =2.0</td>
<td>4.0</td>
<td>&gt; or =8</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt; or =8.0</td>
<td>16</td>
<td>&gt; or =32</td>
</tr>
</tbody>
</table>
Amikacin  No Interpretations available
Ethambutol  No Interpretations available
Rifabutin  No Interpretations available
Rifampin  No Interpretations available
Streptomycin  No Interpretations available

Interpretative criteria for Mycobacterium kansasii and other slowly growing mycobacteria

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mcg/mL) for each interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt; or =32</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =16</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>&lt; or =4</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>No Interpretations available</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt; or =16</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>No Interpretations available</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt; or =2/38</td>
</tr>
</tbody>
</table>

Interpretative criteria for Mycobacterium marinum

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mcg/mL) for each interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt; or =32</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =16</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>&lt; or =4</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>&lt; or =4</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt; or =2/38</td>
</tr>
</tbody>
</table>

**Clinical References:**
Antimicrobial Susceptibility, Aerobic Bacteria, MIC

Clinical Information: Antimicrobial susceptibility testing (AST) determines the minimum inhibitory concentration (MIC) (of a series of increasing concentrations) of antimicrobial incorporated in agar plates, which inhibits the growth of bacteria inoculated on the surface of the agar. Prior studies have determined a breakpoint or MIC value for each antimicrobial, above which the bacterium being tested is considered resistant to that agent. The most important factor contributing to the determination of the breakpoint is probably the expected serum concentration of antimicrobial achieved after giving the usual dosage. The category result (susceptible or resistant) provided along with the MIC is determined by comparing the MIC result with the breakpoint. AST should be performed on pure culture isolates of pathogenic (or potentially pathogenic in special situations) bacteria grown from specimens that have been appropriately collected so as not to confuse clinically significant isolates with normal flora.

Useful For: Determining the in vitro susceptibility of aerobic bacteria involved in human infections

Interpretation: A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested.

Reference Values:
Results are reported as minimum inhibitory concentration (MIC) in mcg/mL and as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Susceptible (S)
The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used.

Susceptible-Dose Dependent (D)
The "susceptible-dose dependent" category implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results are in the D category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved dosage regimen, because higher exposure gives the highest probability of adequate coverage of a D isolate. The drug label should be consulted for recommended doses and adjustment for organ function. The D category may be assigned when doses well above those used to calculate the susceptible breakpoint are approved and used clinically.

Intermediate (I)
The "intermediate" category includes isolates with antimicrobial agent minimum inhibitory concentrations (MIC) that approach usually attainable blood and tissue levels, and for which response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant (R)
The "resistant" category implies that the isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Nonsusceptible (NS)
The "nonsusceptible" category is used for isolates for which only a susceptible interpretive criterion has been designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above the value indicated for the susceptible breakpoint are reported as nonsusceptible.
Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

(CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. CLSI document M100-S25. Wayne, PA, Clinical and Laboratory Standards Institute, 2015)


Antimicrobial Susceptibility, Anaerobic Bacteria, MIC

Clinical Information: Anaerobic bacteria make up a large part of the human body’s normal flora and generally do not cause infection. When usual skin and mucosal barriers are penetrated and in an anaerobic environment, these bacteria can behave as pathogens. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes and by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and they are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians.

Useful For: Determining the in vitro susceptibility of anaerobic bacteria involved in human infections

Interpretation: A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested.

Reference Values:

Results are reported as minimum inhibitory concentration (MIC) in mcg/mL and as susceptible, susceptible dose dependent, intermediate, or resistant according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Vancomycin, ciprofloxacin, and minocycline are reported as MIC values only (without interpretations).

Susceptible (S):
The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used.

Susceptible-Dose Dependent (D):
The "susceptible-dose dependent" category implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results are in the D category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved dosage regimen, because higher exposure gives the highest probability of adequate coverage of a D isolate. The drug label should be consulted for recommended doses and adjustment for organ function. The D category may be assigned when doses well above those used to calculate the susceptible breakpoint are approved and used clinically.

Intermediate (I):
The "intermediate" category includes isolates with antimicrobial agent minimum inhibitory concentrations (MIC) that approach usually attainable blood and tissue levels, and for which response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a
drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant (R):
The "resistant" category implies that the isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Nonsusceptible (N):
The "nonsusceptible" category is used for isolates for which only a susceptible interpretive criterion has been designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above the value indicated for the susceptible breakpoint is reported as nonsusceptible.

Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set. (CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. CLSI document M100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; 2015)


**Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line**

**Clinical Information:** Primary treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide. Susceptibility testing of each Mycobacterium tuberculosis complex isolate against these first-line antimycobacterial agents is a key component of patient management. In vitro susceptibility testing methods are available to assess the susceptibility of Mycobacterium tuberculosis complex isolates to selected antimycobacterial agents. The Clinical Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility testing results. Current recommendations indicate that laboratories should use a rapid broth method in order to obtain Mycobacterium tuberculosis susceptibility data as quickly as possible to help guide patient management. Resistance, as determined by rapid testing, must be confirmed by another method or by another laboratory. This test uses an FDA-cleared commercial system for rapid broth susceptibility testing of Mycobacterium tuberculosis complex and assesses resistance to the following antimycobacterial drugs at the critical concentrations indicated: isoniazid (0.1 mcg/mL and 0.4 mcg/mL), rifampin (1 mcg/mL), and ethambutol (5 mcg/mL and 8 mcg/mL). A separate test is available for testing of the other first-line agent pyrazinamide.

**Useful For:** Rapid, qualitative susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture Affirming the initial choice of chemotherapy for Mycobacterium tuberculosis infections Confirming the emergence of drug resistance Guiding the choice of alternate agents for therapy for Mycobacterium tuberculosis infections

**Interpretation:** Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to the aforementioned drugs at the critical concentrations. Some experts believe that patients infected with strains exhibiting resistance to low levels of isoniazid (0.1 mcg/mL) but not exhibiting resistance to high levels (0.4 mcg/mL) may benefit from continuing therapy with this agent. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate therapeutic regimen and dosages.

**Reference Values:**
Results are reported as susceptible or resistant.


**MMLNS 82019**

**Antimicrobial Susceptibility, Nocardia species**

**Clinical Information:** Nocardia asteroides, the most commonly recognized aerobic actinomycete, causes significant disease in immunocompromised patients. Clinical presentations can include pneumonia, skin abscess, bacteremia, brain abscess, eye infection, and joint infection. Other species associated with human disease include Nocardia brasiliensis, Nocardia otitidiscaviarum, Nocardia farcinica, Nocardia nova, and Nocardia transvalensis. Treatment usually consists of trimethoprim-sulfamethoxazole, sometimes in combination with other antimicrobials, such as amikacin. However, some patients develop drug allergy, others develop resistant isolates due to noncompliance, and some antimicrobials penetrate the central nervous system better than others. Therefore, the selection of appropriate agents becomes extremely important to patient outcome.

**Useful For:** Determining the resistance of species of Nocardia and other aerobic actinomycetes to antimicrobial agents

**Interpretation:** Interpretive values for susceptibility testing of Nocardia species using a broth microdilution method. (Values expressed in mcg/mL): Antimicrobial Agent Interpretations S I R

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Concentration Range</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim/Sulfamethoxazole(3)</td>
<td>0.25/4.75-8/152</td>
<td>&lt; or =2/38 - &gt; or =4/76</td>
</tr>
<tr>
<td>Linezolid(2)</td>
<td>1-32</td>
<td>&lt; or =8 - -</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.12-4</td>
<td>&lt; or =1 2 &gt; or =4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2-64</td>
<td>&lt; or =4 8 &gt; or =16</td>
</tr>
<tr>
<td>Moxifloxacin(1,3)</td>
<td>0.25-8</td>
<td>- - -</td>
</tr>
<tr>
<td>Cefepime(3)</td>
<td>1-32</td>
<td>&lt; or =8 16 &gt; or =32</td>
</tr>
<tr>
<td>Augmentin(3)</td>
<td>2/1-64/32</td>
<td>&lt; or =8/4 16/8 &gt; or =32/16</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1-64</td>
<td>&lt; or =8 - -</td>
</tr>
<tr>
<td>Ceftriaxone(3)</td>
<td>4-64</td>
<td>&lt; or =8 16-32 &gt; or =64</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0.12-16</td>
<td>&lt; or =1 2-4 &gt; or =8</td>
</tr>
<tr>
<td>Minocycline(3)</td>
<td>1-8</td>
<td>&lt; or =1 2-4 &gt; or =8</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1-16</td>
<td>&lt; or =4 8 &gt; or =16</td>
</tr>
</tbody>
</table>

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Antimullerian Hormone (AMH), Serum

Clinical Information: Antimullerian hormone (AMH), also known as mullerian-inhibiting substance, is a dimeric glycoprotein hormone belonging to the transforming growth factor-beta family. It is produced by Sertoli cells of the testis in males and by ovarian granulosa cells in females. Expression during male fetal development prevents the mullerian ducts from developing into the uterus, resulting in development of the male reproductive tract. In the absence of AMH, the Mullerian ducts and structures develop into the female reproductive tract. In males, AMH serum concentrations are elevated in males under 2 years old and then progressively decrease until puberty, when there is a sharp decline. In females, AMH is produced by the granulosa cells of small growing follicles from the 36th week of gestation onwards until menopause when levels become undetectable. Because of the gender differences in AMH concentrations, its changes in circulating concentrations with sexual development, and its specificity for Sertoli and granulosa cells, measurement of AMH has utility in the assessment of gender, gonadal function, fertility, and as a gonadal tumor marker. Since AMH is produced continuously in the granulosa cells of small follicles during the menstrual cycle, it is superior to the episodically released gonadotropins and ovarian steroids as a marker of ovarian reserve. Furthermore, AMH concentrations are unaffected by pregnancy or use of oral or vaginal estrogen- or progestin-based contraceptives. Studies in fertility clinics have shown that females with higher concentrations of AMH have a better response to ovarian stimulation and tend to produce more retrievable oocytes than females with low or undetectable AMH. Females at risk of ovarian hyperstimulation syndrome after gonadotropin administration can have significantly elevated AMH concentrations. Polycystic ovarian syndrome can elevate serum AMH concentrations because it is associated with the presence of large numbers of small follicles. AMH measurements are commonly used to evaluate testicular presence and function in infants with intersex conditions or ambiguous genitalia, and to distinguish between cryptorchidism (testicles present but not palpable) and anorchia (testicles absent) in males. In minimally virilized phenotypic females, AMH helps differentiate between gonadal and nongonadal causes of virilization. Serum AMH concentrations are increased in some patients with ovarian granulosa cell tumors, which comprise approximately 10% of ovarian tumors. AMH, along with related tests including inhibin A and B (INHA / Inhibin A, Tumor Marker, Serum; INHB / Inhibin B, Serum; INHAB / Inhibin A and B, Tumor Marker, Serum), estradiol (EEST / Estradiol, Serum), and CA-125 (CA25 / Cancer Antigen 125 [CA 125], Serum), can be useful for diagnosing and monitoring these patients.

Useful For: Assessment of menopausal status, including premature ovarian failure Assessing ovarian...
status, including ovarian reserve and ovarian responsiveness, as part of an evaluation for infertility and assisted reproduction protocols such as in vitro fertilization Assessing ovarian function in patients with polycystic ovarian syndrome Evaluation of infants with ambiguous genitalia and other intersex conditions Evaluating testicular function in infants and children Monitoring patients with antimullerian hormone-secreting ovarian granulosa cell tumors

**Interpretation:** Menopausal women or women with premature ovarian failure of any cause, including after cancer chemotherapy, have very low antimullerian hormone (AMH) levels, often below the current assay detection limit of 0.1 ng/mL. While the optimal AMH concentrations for predicting response to in vitro fertilization are still being established, it is accepted that AMH concentrations in the perimenopausal to menopausal range indicate minimal to absent ovarian reserve. Depending on patient age, ovarian stimulation is likely to fail in such patients By contrast, if serum AMH concentrations exceed 3 ng/mL, hyper-response to ovarian stimulation may result. For these patients, a minimal stimulation would be recommended. In patients with polycystic ovarian syndrome, AMH concentrations may be 2- to 5-fold higher than age-appropriate reference range values. Such high levels predict anovulatory and irregular cycles. In children with intersex conditions, an AMH result above the normal female range is predictive of the presence of testicular tissue, while an undetectable value suggests its absence. In boys with cryptorchidism, a measurable AMH concentration is predictive of undescended testes, while an undetectable value is highly suggestive of anorchia or functional failure of the abnormally sited gonad. Granulosa cell tumors of the ovary may secrete AMH, inhibin A, and inhibin B. Elevated levels of any of these markers can indicate the presence of such a neoplasm in a woman with an ovarian mass. Levels should fall with successful treatment. Rising levels indicate tumor recurrence or progression.

**Reference Values:**

**Males**
- <24 months: 14-466 ng/mL
- 24 months-12 years: 7.4-243 ng/mL
- >12 years: 0.7-19 ng/mL

**Females**
- <24 months: <4.7 ng/mL
- 24 months-12 years: <8.8 ng/mL
- 13-45 years: 0.9-9.5 ng/mL
- >45 years: <1.0 ng/mL

**Clinical References:**

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**Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum**

**Clinical Information:** Antineutrophil cytoplasmic antibodies (ANCA) occur in patients with autoimmune vasculitis including Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), or organ-limited variants thereof such as pauci-immune necrotizing glomerulonephritis.(1) ANCA react with enzymes in the cytoplasmic granules of human neutrophils including proteinase 3 (PR3), myeloperoxidase (MPO), elastase, and cathepsin G. Autoantibodies to PR3 occur in patients with WG (both classical WG and WG with limited end-organ involvement) and produce a characteristic pattern of granular cytoplasmic fluorescence on ethanol-fixed neutrophils called the cANCA pattern. Antibodies to MPO occur predominately in patients with MPA and produce a pattern of perinuclear cytoplasmic fluorescence on ethanol-fixed neutrophils called the pANCA pattern. Autoantibodies to PR3 and MPO can also be detected by EIA methods and are referred to as PR3 ANCA and MPO ANCA, respectively.

**Useful For:** Evaluating patients suspected of having autoimmune vasculitis, both Wegener's granulomatosis and microscopic polyangiitis

**Interpretation:** Positive results for proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCA) and cANCA or pANCA are consistent with the diagnosis of Wegener's granulomatosis (WG), either systemic WG with respiratory and renal involvement or limited WG with more restricted end-organ involvement.
involvement. Positive results for MPO ANCA and pANCA are consistent with the diagnosis of autoimmune vasculitis including microscopic polyangiitis (MPA) or pauci-immune necrotizing glomerulonephritis. A positive result for PR3 ANCA or MPO ANCA has been shown to detect 89% of patients with active WG or MPA (with or without renal involvement) with fewer than 1% false-positive results in patients with other diseases.(1)

**Reference Values:**

**MYELOPEROXIDASE ANTIBODIES, IgG**

- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- > or =1.0 U (positive)

Reference values apply to all ages.

**PROTEINASE 3 ANTIBODIES, IgG**

- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- > or =1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


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**Antinuclear Antibodies (ANA), HEP-2 Substrate, Serum**

**Clinical Information:** Antinuclear antibodies (ANA) occur in patients with various autoimmune diseases, both systemic and organ specific, but they are particularly common in systemic rheumatic diseases (SRD). The SRDs include systemic lupus erythematosus, discoid lupus erythematosus, drug-induced lupus erythematosus, mixed connective tissue disease, Sjogrenâ€™s syndrome, scleroderma (systemic sclerosis), CREST syndrome (calcinosis, Raynaudâ€™s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), rheumatoid arthritis, and polymyositis or dermatomyositis. ANA can be detected by a number of various technologies, including indirect immunofluorescence, enzyme immunoassays, and bead-based multiplex immunoassays.

**Useful For:** Diagnosis of autoimmune diseases

**Interpretation:** Midbody is a rare pattern found to occur in scleroderma and Raynaudâ€™s phenomenon. Cytoplasmic Staining is associated with antibodies that may be derived from multiple cytoplasmic proteins including Jo-1 (20%-40% polymyositis), ribosome P (10%-15% systemic lupus erythematosus [SLE]), and mitochondrial M2 (90% PBC and 40% scleroderma). Other Cytoplasmic Patterns Mitotic Spindle pattern is nonspecific and can be seen in a variety of disease states; has no known clinical significance. Centrosome (Centriole) is a rare pattern that may be seen in patients with nonspecific rheumatic diseases and some chronic post-viral syndromes. Golgi Apparatus is observed in patients with SLE, Sjogren's syndrome, mixed connective tissue disease, and is seen in 30% to 80% of rheumatoid arthritis. If the anti-nuclear antibody screen is positive a titer will be performed if indicated. Low titers of antinuclear antibodies reactivity are observed in approximately 5% of apparently healthy individuals and the incidence increases with increasing age. The results of this test must be interpreted in the context of the clinical picture. Interpretive comments are provided when applicable.

**Reference Values:**

<1:40 (Negative)

**Clinical References:** This test is a laboratory diagnostic aid and by itself is not diagnostic. Positive results with this test may occur in apparently healthy people. Therefore, the results of this test must be interpreted by a medical authority in the context of the patient's total clinical condition. Sera from systemic lupus erythematosus patients undergoing steroid therapy may give negative results. No definitive
association between the pattern of nuclear fluorescence and any specific disease state is intended with this test. Many drugs (eg, hydralazine, procainamide) may induce antinuclear antibodies production.

**Antinuclear Antibodies (ANA), IFA with Reflex to Connective Tissue Disease Antibodies**

**Clinical Information:** Antinuclear antibodies (ANA) occur in patients with various autoimmune diseases, both systemic and organ specific, but they are particularly common in systemic rheumatic diseases (SRD). The SRDs include systemic lupus erythematosus (SLE), discoid lupus erythematosus, drug-induced lupus erythematosus, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), CREST syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), rheumatoid arthritis, and polymyositis or dermatomyositis. Autoantibodies with High Specificity for Individual Connective Tissue Diseases dsDNA antibodies SLE Scl 70 antibodies (topoisomerase I) Scleroderma Jo 1 antibodies (histidyl tRNA synthetase) Polymyositis SSA/Ro and SSB/La antibodies Sjogren syndrome RNP antibodies (in isolation) MCTD Sm antibodies SLE Ribosome P antibodies SLE Low titers of ANA reactivity are observed in approximately 5% of apparently healthy individuals and the incidence increases with increasing age. Titers > or =1:160 are generally considered to be clinically significant and more closely related to the presence of active disease. The results of this test must be interpreted in the context of the clinical picture.

**Useful For:** Evaluation of patients with signs and symptoms compatible with connective tissue diseases The testing algorithm is useful in the initial evaluation of patients and performs best in clinical situations in which the prevalence of disease is low.

**Interpretation:** Interpretive comments are provided. See individual test IDs for additional information.

**Reference Values:**
- <1:40 (Negative)

**Clinical References:**

**Antinuclear Antibodies (ANA), Serum**

**Clinical Information:** Measurement of antinuclear antibodies (ANAs) in serum is the most commonly performed screening test for patients suspected of having a systemic rheumatic disease, also referred to as connective tissue disease.(1) ANAs occur in patients with a variety of autoimmune diseases, both systemic and organ-specific. They are particularly common in the systemic rheumatic diseases, which include lupus erythematosus (LE), discoid LE, drug-induced LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), CREST (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome, polymyositis/dermatomyositis, and rheumatoid arthritis.(1) The diagnosis of a systemic rheumatic disease is based primarily on the presence of compatible clinical signs and symptoms. The results of tests for autoantibodies including ANA and specific autoantibodies are ancillary. Additional diagnostic criteria include consistent histopathology or specific radiographic findings. Although individual systemic rheumatic diseases are relatively uncommon, a great many patients present with clinical findings that are compatible with a systemic rheumatic disease and large numbers of tests for ANA are ordered to eliminate the possibility of a systemic rheumatic disease. See Connective Tissue Diseases Cascade Test-Ordering Algorithm in Special Instructions, also see Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients suspected of having a systemic rheumatic disease
**Interpretation:** A large number of healthy individuals have weakly-positive antinuclear antibody (ANA) results, many of which are likely to be clinical false-positives; therefore, second-order testing of all positive ANAs yields a very low percentage of positive results to the specific nuclear antigens. A positive ANA result at any level is consistent with the diagnosis of systemic rheumatic disease, but a result > or =3.0 U is more strongly associated with systemic rheumatic disease than a weakly-positive result. Positive ANA results >3.0 U are associated with the presence of detectable autoantibodies to specific nuclear antigens. The nuclear antigens are associated with specific diseases (eg, anti-Scl 70 is associated with scleroderma) and can be detected with second-order testing.

**Reference Values:**
< or =1.0 U (negative)
1.1-2.9 U (weakly positive)
3.0-5.9 U (positive)
> or =6.0 U (strongly positive)
Reference values apply to all ages.

**Clinical References:**

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**Antistrep-O Titer, Serum**

**Clinical Information:** A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

**Useful For:** Demonstration of acute or recent streptococcal infection

**Interpretation:** Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test such as anti-DNase B is recommended.

**Reference Values:**
<5 years: < or =70 IU/mL
5-17 years: < or =640 IU/mL
> or =18 years: < or =530 IU/mL

Antithrombin Activity, Plasma

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa. Heparin and certain other naturally occurring glycosaminoglycans markedly enhance antithrombin's anticoagulant activity (approximately 1,000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of heparin's anticoagulant activity. The antithrombin gene on chromosome 1 encodes a glycoprotein of approximately 58,000 molecular weight that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 umol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]) with the potential of development as early as adolescence or younger adulthood. More than 100 different mutations have been identified throughout the gene producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen). Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2,000 to 1:3,000 in general populations, although minor deficiency (antithrombin activity = 70%-75%) may be more frequent (approximately 1:350-650). In populations with venous thrombophilia, approximately 1% to 2% have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C [APC]-resistance [factor V Leiden mutation]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (e.g., stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS). Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) or with nephritic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions (1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe DIC/IFC is being evaluated. Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

Useful For: Diagnosis of antithrombin deficiency, acquired or congenital Monitoring treatment of antithrombin deficiency disorders, including infusion of antithrombin therapeutic concentrate

Interpretation: Antithrombin deficiencies due to inherited causes are much less common than those due to acquired causes (see Clinical Information). Diagnosis or hereditary deficiency requires clinical correlation, with the prospect of repeat testing (including antithrombin antigen assay) and family studies (with appropriate counseling). DNA-based diagnostic testing may be helpful, but is not readily available. The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations. Antithrombin deficiency, acquired or congenital, may contribute to the phenomenon of "heparin therapy resistance" (requirement of larger heparin doses than expected for achievement of therapeutic anticoagulation responses). However, it may more often have other pathophysiology, such as "acute-phase" elevation of coagulation factor VIII or plasma heparin-binding proteins. Increased antithrombin activity has no definite clinical significance.

Reference Values:
> or =6 months-adults: 80-130%
Normal, full-term newborn infants may have decreased levels (> or =35-40%), which reach adult levels by 90 days postnatal.*
Healthy, premature infants (30-36 weeks gestation) may have decreased levels which reach adult levels by 180 days postnatal.*
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**

**Antithrombin Antigen, Plasma**

**Clinical Information:** Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance antithrombin's anticoagulant activity (approximately 1,000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of heparin's anticoagulant activity. The antithrombin gene on chromosome 1 encodes a glycoprotein of approximately 58,000 molecular weight that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 umol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare, autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism), with the potential of development as early as adolescence or younger adulthood. More than 100 different mutations have been identified throughout the gene, producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2,000 to 1:3,000 in general populations, although minor deficiency (antithrombin activity =70% to 75%) may be more frequent (approximately 1:350 to 1:650). In populations with venous thrombophilia, approximately 1% to 2% have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C [APC]-resistance [factor V Leiden mutation]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency may occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) -Nephritic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe DIC/IFC is being evaluated.(4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

**Useful For:** Assessing abnormal results of the antithrombin activity assay. (ATTF / Antithrombin
Activity, Plasma), which is recommended as the primary (screening) antithrombin assay. Diagnosing antithrombin deficiency, acquired or congenital, in conjunction with measurement of antithrombin activity as an adjunct in the diagnosis and management of carbohydrate-deficient glycoprotein syndromes.

**Interpretation:** Hereditary antithrombin deficiency is much less common than acquired deficiency. Diagnosis of hereditary deficiency requires clinical correlation, testing of both antithrombin activity and antithrombin antigen, and may be aided by repeated testing and by family studies. DNA-based diagnostic testing may be helpful, but is generally not readily available. Acquired antithrombin deficiency may occur in association with a number of conditions (see Clinical Information). The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations. Increased antithrombin activity has no definite clinical significance.

**Reference Values:**

- Adults: 80-130%
  - Normal, full-term newborn infants may have decreased levels (> or =35-40%) which reach adult levels by 180 days postnatal.*
  - Healthy, premature infants (30-36 weeks gestation) may have decreased levels which reach adult levels by 180 days postnatal.*
- *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**


### APCZ 35418

**APC Gene, Full Gene Analysis**

**Clinical Information:** Familial adenomatous polyposis (FAP) is an autosomal dominant condition caused by mutations in the APC gene located on the long arm of chromosome 5 (5q21). Classic FAP is characterized by progressive development of hundreds to thousands of adenomatous colon polyps. Polyps may develop during the first decade of life and the majority of untreated FAP patients will develop colon cancer by age 40. Typically, there is a predominance of polyps on the left side of the colon, however, other areas of the colon may also be affected. The presence of extracolonic manifestations is variable and includes gastric and duodenal polyps, ampullary polyps, osteomas, dental abnormalities (unerupted teeth), congenital hypertrophy of the retinal pigment epithelium (CHRPE), benign cutaneous lesions, desmoids tumors, hepatoblastoma, and extracolonic cancers. Common constellations of colonic and extracolonic manifestations have resulted in the designation of 3 clinical variants: Gardner syndrome, Turcot syndrome, and hereditary desmoid disease. Gardner syndrome is characterized by colonic polyps of classic FAP with epidermoid skin cysts and benign osteoid tumors of the mandible and long bones. Turcot syndrome is characterized by multiple colonic polyps and central nervous system (CNS) tumors. Turcot syndrome is an unusual clinical variant of FAP, as it is also considered a clinical variant of hereditary nonpolyposis colorectal cancer (HNPPCC). Individuals with Turcot syndrome have CNS tumors in addition to adenomatous polyps. The types of CNS tumor observed helps to distinguish Turcot-FAP variant patients from Turcot-HNPCC variant patients. The predominant CNS tumor associated with the Turcot-FAP variant is medulloblastoma, while glioblastoma is the predominant CNS tumor associated with Turcot-HNPCC. Hereditary desmoid disease (HDD) is a variant of FAP with multiple desmoids tumors as the predominant feature. Many patients with HDD may not even show colonic manifestations of FAP. APC germline testing may assist clinicians in distinguishing a sporadic desmoid tumor, from that associated with FAP. Attenuated FAP (AFAP) is characterized by later onset of disease and a milder phenotype (typically <100 adenomatous polyps and fewer extracolonic manifestations) than classic FAP. Typically individuals with AFAP develop symptoms of the disease at least 10 to 20 years later than...
classically affected individuals. Individuals with AFAP often lack a family history of colon cancer and/or multiple adenomatous polyps. Of note, clinical overlap is observed between AFAP and MYH-associated polyposis (MAP), an autosomal recessive polyposis syndrome typically associated with fewer than 100 polyps. Although the clinical phenotype of MAP remains somewhat undefined, extracolonic manifestations, including CHRPE have been described in affected patients. Given the phenotypic overlap of AFAP and MAP, these tests are commonly ordered together or in a reflex fashion. See Colonic Polyposis Syndromes Testing Algorithm in Special Instructions for additional information. Also see Hereditary Colorectal Cancer: Adenomatous Polyposis Syndromes (September 2004 Communique) in publications for additional information.

**Useful For:** Confirmation of familial adenomatous polyposis (FAP) diagnosis for patients with clinical features

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Apolipoprotein A-I (APOA1) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein A-I, apolipoprotein A-II, fibrinogen alpha chain, gelsolin, cystatin C, and lysozyme. Apolipoprotein A-I, apolipoprotein A-II, lysozyme, and fibrinogen alpha-chain amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Apolipoprotein A-I amyloidosis is also associated with additional organ system involvement, including clinical manifestations in the liver, heart, skin, and larynx. In addition, the G26R APOA1 mutation has been associated with a neuropathic presentation. To date, at least 16 amyloidogenic mutations have been identified within the APOA1 gene. The majority of these are missense mutations, although deletion/insertion mutations have also been described. There is some evidence of genotype-phenotype correlations. Mutations that occur near the amino terminal portion of the protein are more often associated with hepatic and renal amyloidosis, while mutations occurring near the carboxyl terminal portion of the gene are more often associated with cardiac, cutaneous, and laryngeal amyloidosis. The majority of mutations reported to date occur at 1 of 2 hot spots spanning amino acid residues 50 through 93 and 170 through 178. Mutations in the APOA1 gene have also been linked to familial hypoalphalipoproteinemia. Patients carrying 1 APOA1 mutation typically demonstrate reduced levels of high-density lipoprotein (HDL) cholesterol, which is associated with increased risk for coronary artery disease. Comparatively, the presence of 2 APOA1 mutations generally results in complete absence of HDL cholesterol and may include additional clinical features such as xanthomas or corneal opacities. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the
etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnosis of individuals suspected of having apolipoprotein A-I (APOA1) gene-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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Apolipoprotein A-II (APOA2) Gene, Full Gene Analysis

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis, including those that encode transthyretin, apolipoprotein A-I, apolipoprotein A-II, fibrinogen alpha chain, gelsolin, cystatin C, and lysozyme. Apolipoprotein A-I, apolipoprotein A-II, lysozyme, and fibrinogen alpha chain amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Apolipoprotein A-II amyloidosis typically presents as a very slowly progressive disease. Age of onset is highly variable, ranging from adolescence to the fifth decade. To date, all mutations that have been identified within the APOA2 gene occur within the stop codon and result in a 21-residue C-terminal extension of the apolipoprotein A-II protein. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnosis of individuals suspected of having apolipoprotein A-II-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Apolipoprotein A1 and B, Plasma

Clinical Information: Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). Apolipoprotein A1 (ApoA1) is the primary protein associated with high-density lipoprotein (HDL). Both ApoB and ApoA1 are more strongly associated with cardiovascular disease than the corresponding lipoprotein cholesterol fraction (see APLA1 / Apolipoprotein A1, Plasma and APLB / Apolipoprotein B, Plasma). However, the most powerful risk prediction value of these proteins appears to be in their ratio (ie, ApoB:ApoA1). ApoB is present in all atherogenic lipoproteins including LDL, Lp(a), intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL) remnants. ApoA1 is the nucleating protein around which HDL forms during reverse cholesterol transport. Therefore, the ApoB:ApoA1 ratio represents the balance between atherogenic and antiatherogenic lipoproteins. Several large prospective studies have shown that the ApoB:ApoA1 ratio performs as well, and often better, than traditional lipids as an indicator of risk.(1-3)

Useful For: Assessment of residual risk in patients at target non-HDL-C (or LDL-C) Follow-up studies in individuals with non-HDL-C (or LDL-C) values inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors

Interpretation: An elevated apolipoprotein B (ApoB) level confers increased risk of coronary artery disease and can be used as a therapeutic target analogous to non-HDL-C and LDL-C. Risk Category Therapeutic Target: ApoB Non-HDL-C LDL-C Moderate to High <90 mg/dL <130 mg/dL <100 mg/dL Very High <80 mg/dL <100 mg/dL <70 mg/dL Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy. A reduced apolipoprotein A1 (ApoA1) level confers an increased risk of coronary artery disease. Identification of an ApoA1 <25 mg/dL may be helpful in the detection of a genetic disorder such as Tangier disease. An elevated ApoB:ApoA1 ratio confers an increased risk of coronary artery disease.

Reference Values:

<table>
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<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
<th>Apolipoprotein B (mg/dL)</th>
<th>Apolipoprotein B/A1 ratio</th>
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<tbody>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120</td>
<td>Acceptable:</td>
<td>&gt; or =110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>high: 90-109 High:</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt; or =120</td>
<td></td>
</tr>
<tr>
<td>&gt;18 years</td>
<td></td>
<td>Desirable:</td>
<td>Lower Risk: Risk:</td>
</tr>
<tr>
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<td></td>
<td>90-99</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Very high:</td>
<td>Higher Risk:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; or =140</td>
<td>0.9 Females</td>
</tr>
<tr>
<td>Age</td>
<td>Apolipoprotein A (mg/dL)</td>
<td>Apolipoprotein B (mg/dL)</td>
<td>Apolipoprotein B/A1 ratio</td>
</tr>
<tr>
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<td></td>
<td>&gt; or =120</td>
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<td>Lower Risk: Risk:</td>
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<td></td>
<td>90-99</td>
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Apolipoprotein A1, Plasma

Clinical Information: Apolipoprotein A1 (ApoA1) is the primary protein associated with high-density lipoprotein (HDL) particles, and plays a central role in reverse cholesterol transport. (1) HDL cholesterol (HDL-C) and ApoA1 concentrations are inversely related to the risk for coronary artery disease (CAD). (2) There are a variable number of ApoA1 proteins per HDL particle. Therefore, ApoA1 is not a 1:1 surrogate marker for HDL particles. Similarly, the number of ApoA1 proteins and the amount of cholesterol contained in HDL particles is highly variable. This heterogeneity has led to unique clinical findings related to ApoA1 compared with HDL-C. Increased ApoA1 concentrations are more strongly associated with a reduction in risk of a first myocardial infarction than HDL-C concentrations. (3) Low concentrations of ApoA1, but not HDL-C, are predictive of preclinical atherosclerosis as assayed by computed tomography estimated coronary artery calcium (CAC) scoring. (4) Increased ApoA1, but not HDL-C concentrations, are associated with reduced cardiovascular events among statin-treated patients, even when LDL-C <50 mg/dL. (5) In statin-treated patients, patients whose ApoA1 increased while on treatment were at lower risk than those whose ApoA1 did not increase.

Useful For: Evaluation of risk for atherosclerotic cardiovascular disease Helpful to aid in the detection of Tangier disease

Interpretation: Low levels of apolipoprotein A1 (ApoA1) confer increased risk of atherosclerotic cardiovascular disease. ApoA1 <25 mg/dL may aid in the detection of a genetic disorder such as Tangier disease.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years Low: low: 115-120 Acceptable: &gt;120</td>
<td></td>
</tr>
<tr>
<td>&gt;18 years &gt; or =120 Females</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Apolipoprotein A (mg/dL)</td>
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<td></td>
</tr>
<tr>
<td>&gt;18 years &gt; or =140</td>
<td></td>
</tr>
</tbody>
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Clinical References:

**Apolipoprotein B, Plasma**

**Clinical Information:** Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). LDL contains a variable amount of cholesterol, but each LDL contains exactly 1 ApoB protein. Therefore, ApoB is a superior indicator of circulating LDL compared to LDL cholesterol (LDL-C). ApoB has been demonstrated to perform equally with LDL particles measured by nuclear magnetic resonance spectroscopy. (1) ApoB is strongly associated with increased risk of developing cardiovascular disease (CVD) and often outperforms LDL-C at predicting risk of coronary heart disease. (2–4) Patients with acceptable non-HDL-C (or LDL-C) but elevated ApoB remain at higher risk of developing CVD; conversely, patients with acceptably low ApoB but moderate non-HDL-C or LDL-C elevations are at a reduced risk for CVD. (5,6) Finally, in 7 different placebo-controlled randomized clinical trials, on-statin reduction of ApoB was more closely related to CVD risk reduction than non-HDL-C or LDL-C. (7)

**Useful For:** Assessment of residual risk in patients at target non high-density lipoprotein-cholesterol (HDL-C) (or low-density lipoprotein-cholesterol: LDL-C) Follow-up studies in individuals with non-HDL-C (or LDL-C) values inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors Confirmation of suspected abetalipoproteinemia or hypobetalipoproteinemia

**Interpretation:** Elevated ApoB confers increased risk of coronary artery disease ApoB can be used as a therapeutic target analogous to non-HDL-C and LDL-C. Risk Category Therapeutic Target: ApoB Non-HDL-C LDL-C Moderate to High <90 mg/dL <130 mg/dL <100 mg/dL Very High <80 mg/dL <100 mg/dL <70 mg/dL Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy.

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<tr>
<th>Age</th>
<th>Apolipoprotein B (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Acceptable: high 90-109</td>
</tr>
<tr>
<td></td>
<td>High: &gt; or =110</td>
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<td>&gt;18 years</td>
<td>Desirable: Desirable 90-99</td>
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<td></td>
<td>Very high: 120-139</td>
</tr>
<tr>
<td></td>
<td>Extremely high: &gt; or =140</td>
</tr>
</tbody>
</table>

Apolipoprotein B-100 Molecular Analysis, R3500Q and R3500W

Clinical Information: Autosomal dominant hypercholesterolemia (ADH) is characterized by high levels of LDL cholesterol and associated with premature cardiovascular disease and myocardial infarction. The majority of ADH is caused by genetic variants that lead to decreased intracellular uptake of cholesterol. Approximately 1 in 500 individuals worldwide are affected by ADH and 15% of individuals with ADH have familial defective apolipoprotein B-100 (FDB) due to variants in the LDL receptor-binding domain of the APOB gene, which maps to chromosome 2p and encodes for apolipoprotein B-100. FDB can occur in either the heterozygous or homozygous state, with the latter expressing more severe disease. Approximately 40% of males and 20% of females with an APOB mutation will develop coronary artery disease. The vast majority of FDB cases are caused by a single APBO variant at residue 3500, resulting in a glutamine substitution for the arginine residue (R3500Q). This common FDB variant occurs at an estimated frequency of 1:500 individuals of European descent. Another, less frequently occurring variant at that same codon results in a tryptophan substitution, R3500W, and is more prevalent in individuals of Chinese and Malay descent, but has been identified in the Scottish population as well. The R3500W variant is estimated to occur in approximately 2% of ADH cases. Residue 3500 interacts with other apolipoprotein B-100 residues to induce conformational changes necessary for apolipoprotein B-100 binding to the LDL receptor. Thus, variants at residue 3500 lead to a reduced binding affinity of LDL for its receptor. There is a high degree of phenotypic overlap between FDB and familial hypercholesterolemia (FH), the latter due to variants in LDLR, which encodes for the LDL receptor (LDLR). In general, individuals with FDB have less severe hypercholesterolemia, fewer occurrences of tendinous xanthomas, and a lower incidence of coronary artery disease, compared with FH. Plasma LDL cholesterol levels in patients with homozygous FDB are similar to levels found in patients with heterozygous (rather than homozygous) FH. Identification of APOB variants in individuals suspected of having ADH helps to obtain a definitive diagnosis of the disease as well as determine appropriate treatment. Therapy for FDB is aimed at lowering the plasma levels of LDL, and both heterozygotes and homozygotes generally respond well to statins. Screening of at-risk family members allows for effective primary prevention by instituting statin therapy and dietary modifications at an early stage.

Useful For: Aiding in the diagnosis of familial defective apolipoprotein B-100 in individuals with elevated untreated LDL cholesterol concentrations
Distinguishing the diagnosis of familial defective apolipoprotein B-100 from other causes of hyperlipidemia, such as familial hypercholesterolemia and familial combined hyperlipidemia
Comprehensive genetic analysis for hypercholesterolemic individuals who test negative for a variant in the LDLR gene by sequencing (LDLRS / Familial Hypercholesterolemia, LDLR Full Gene Sequencing) and/or gene dosage (LDLM / Familial Hypercholesterolemia, LDLR Large Deletion/Duplication, Molecular Analysis)

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

roles in blood lipid metabolism. Defects in apolipoprotein E (Apo E) are responsible for familial dysbetalipoproteinemia, or type III hyperlipoproteinemia, in which increased plasma cholesterol and triglycerides result from impaired clearance of chylomicron and very-low-density lipoprotein (VLDL) remnants. The human APOE gene is located on chromosome 19. The 3 common APOE alleles are designated e2, e3, and e4, which encode the Apo E isoforms E2, E3, and E4, respectively. E3, the most common isoform in Caucasians, shows cysteine (Cys) at amino acid position 112 and arginine (Arg) at position 158. E2 and E4 differ from E3 by single amino acid substitutions at positions 158 and 112, respectively (E2: Arg158->Cys; E4: Cys112->Arg). The allele frequencies for most Caucasian populations are as follows: -e2=8% to 12% -e3=74% to 78% -e4=14% to 15% E2 and E4 are both associated with higher plasma triglyceride concentrations. Over 90% of individuals with type III hyperlipoproteinemia are homozygous for the e2 allele. However, <10% of individuals homozygous for the e2 allele have overt type III hyperlipoproteinemia. This suggests that other genetic, hormonal, or environmental factors must contribute to the phenotypic expression of the disease. The e4 allele has been linked to pure elevations of low-density lipoproteins (LDL). Patients with a lipid profile consistent with type III hyperlipidemia are candidates for analysis of their APOE genotype. The APOE gene is also a known susceptibility gene for Alzheimer disease. The e4 allele is associated with an increased risk for Alzheimer disease, particularly late-onset disease, in a dose-dependent manner. This risk is also influenced by other factors. It is estimated that individuals with the APOE e3/e4 genotype have a 4-fold relative risk for Alzheimer disease, while homozygotes for e4 allele have a 12-fold relative risk. Several studies have suggested a protective effect of the APOE e2 allele. The APOE e4 allele, however, is neither sufficient nor necessary for the development of Alzheimer disease. Approximately 50% of individuals with Alzheimer disease carry an e4 allele and many individuals who have an e4 allele will never develop Alzheimer disease. The use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

**Useful For:** Determining the specific apolipoprotein E (APOE) genotypes in patients with type III hyperlipoproteinemia APOE genotyping has been used to assess susceptibility for Alzheimer disease. However, the use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

**FAPLG**

**Apple IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to
select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Apple, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Apricot, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for...
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
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<td>50.0-99.9</td>
<td>Strongly positive</td>
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<tr>
<td>&gt;5</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

minority of infected individuals, it is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis (SLE): Areas of outbreaks of SLE since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis (WEE): The virus that causes WEE is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons and SLE in older persons. Serious California (LaCrosse) virus infections primarily involve children, especially boys. Adult males exposed to California viruses have high prevalence rates of antibody but usually show no serious illness. Infection among males is primarily due to working conditions and sports activities taking place where the vector is present.

Useful For: Aiding the diagnosis of arboviral (California [LaCrosse], St. Louis encephalitis, Eastern equine encephalitis, and Western equine encephalitis virus) encephalitis

Interpretation: In patients infected with these or related viruses, IgG antibody is generally detectable with in 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. A single serum specimen IgG > or =1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States, it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity.

Reference Values:

CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

EASTERN EQUINE ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

ST. LOUIS ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.
WESTERN EQUINE ENCEPHALITIS
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.


Arbovirus Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: California (LaCrosse) Virus: California (LaCrosse) virus is a member of bunyaviridae and it is 1 of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children younger than 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, last 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis (EEE): EEE is within the alphavirus group. It is a low-prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals, and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis (SLE): Areas or outbreaks of SLE since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis (WEE): The virus that causes WEE is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected,
the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons and SLE in older persons. Serous California (LaCrosse) virus infections primarily involve children, especially boys. Adult males exposed to California viruses have high-prevalence rates of antibody but usually show no serious illness. Infections among males is primarily due to working conditions and sports activities taking place where the vector is present.

**Useful For:** Aiding the diagnosis of arboviral (California [LaCrosse], St. Louis, Eastern equine, and Western equine virus) encephalitis

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

**Reference Values:**

**CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY**
- IgG: <1:10
- IgM: <1:10
- Reference values apply to all ages.

**EASTERN EQUINE ENCEPHALITIS ANTIBODY**
- IgG: <1:10
- IgM: <1:10
- Reference values apply to all ages.

**ST. LOUIS ENCEPHALITIS ANTIBODY**
- IgG: <1:10
- IgM: <1:10
- Reference values apply to all ages.

**WESTERN EQUINE ENCEPHALITIS**
- IgG: <1:10
- IgM: <1:10
- Reference values apply to all ages.

**Clinical References:**

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**AVP 80344**

**Arginine Vasopressin, Plasma**

**Clinical Information:** Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a hypothalamic polypeptide that is transported along the axons of the synthesizing neurons into the posterior pituitary gland. From there it is released into the systemic circulation after appropriate stimuli. The main regulators of AVP secretion are osmotic stimuli, provided by osmoreceptors located in the anteromedial hypothalamus, and volume stimuli, provided by receptors in neck vessels and heart. Under physiological conditions, volume stimuli always override osmotic stimuli. The absence or presence of AVP is the major physiologic determinant of urinary free water excretion or retention. AVP acts principally on renal collecting tubules to increase water reabsorption. The antidiuretic effects of AVP are mediated by V2 vasopressin receptors. AVP can also increase vascular resistance through stimulation of V1 receptors. Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmol stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI). AVP can also be secreted inappropriately in certain...
situations, particularly in elderly patients, leading to water retention and dilutional hyponatremia. Inappropriate AVP secretion might be observed with central nervous system pathology, such as head injury, stroke, or cerebral tumor, or as a side effect of central acting drugs that interfere with the hypothalamic regulation or AVP. Noncentral causes of inappropriate AVP secretion include peripheral stimuli that mimic central vascular hypovolemia, in particular severe low-output cardiac failure, and ectopic AVP secretion (usually by a bronchogenic carcinoma).

**Useful For:** Diagnosis and characterization of diabetes insipidus Diagnosis of psychogenic water intoxication As an adjunct in the diagnosis of syndrome of inappropriate secretion of antidiuretic hormone secretion (SIADH), including ectopic arginine vasopressin production

**Interpretation:** Central diabetes insipidus (DI) can be differentiated from nephrogenic DI by measuring arginine vasopressin (AVP) during a state of maximal, or near maximal, stimulus for AVP release (water deprivation test: perform under medical supervision; stop once plasma osmolality >295 mOsm/kg water or > or =5% loss in body weight) and assessing the antidiuretic response to exogenous administration of the AVP at the conclusion of a water deprivation test: -If AVP is low despite elevated serum osmolality, and the urine osmolality increases significantly after administration of exogenous AVP, the diagnosis is compatible with central DI. -If stimulated AVP is elevated and the administration of exogenous AVP results in little or no increase in urine concentration, the patient likely has nephrogenic DI. -Mixed forms of DI can exist, and both central and peripheral DI may be incomplete, complicating the interpretation of results. Patients with psychogenic polydipsia will either have a normal response to water deprivation or, in particular in long-standing cases, will show a pattern suggestive of mild nephrogenic DI due to loss of concentrating gradient across the nephron as a result of salt-washout by long-standing polydipsia. An elevated plasma AVP level in a hyponatremic, euvolemic patient might be indicative of SIADH. Confirmation of euvolemia is critical in such patients, since an elevated AVP level represents a physiological response to hypovolemia. Seizures, cerebral hemorrhages, cerebral trauma, cerebral tumors, neurosurgery, electroconvulsive therapy, central nervous system acting drugs, and a variety of conditions that reduce apparent blood volume or pressure in central vessels (eg, severe low output cardiac failure) can all result in inappropriate AVP elevations. Depending on the clinical course, these might be short lived. If none of these conditions is present, ectopic AVP secretion, most commonly caused by bronchial carcinoma, should be suspected.

**Reference Values:**
Adults: <1.7 pg/mL
Reference values were determined on platelet-poor EDTA plasma from individuals fasting no longer than overnight.


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**FARI**
57112

Aripiprazole (Abilify)

**Reference Values:**
Units: ng/mL

Expected steady state plasma levels in patients receiving recommended daily dosages: 109.0 - 585.0 ng/mL

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**FARIX**
57123

Arixtra (Fondaparinux) Level

**Interpretation:** Interpretive comments: Dosing protocols for Arixtra (fondaparinux) have been validated by empiric clinical trials. The relationship between pharmacokinetic parameters and either efficacy or safety (bleeding) is not well defined. Peak levels are generally drawn 3-4 hours after drug administration. Fondaparinux plasma concentrations have been reported to range from 0.1 to 0.5 mg/L for adult patients on thromboprophylaxis and from 0.6 to 1.5 mg/L for adults on therapeutic doses (Depasse F, et al, J Thromb Haemost 2004; 2:346-8). A therapeutic level of 0.5-1.0 mg/L has been suggested in a pediatric study (Young G, et al. Pediatric Blood Cancer 2011; 57:1049-54).
Reference Values:
Units: mg/L

ARVGP 63160

Arrhythmogenic Cardiomyopathy Multi-Gene Panel, Blood

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). Arrhythmogenic right ventricular dysplasia (ARVD or AC), is characterized by breakdown of the myocardium and replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. The incidence of ARVC is approximately 1 in 1,000 to 1 in 2,500. Age of onset and severity are variable, but symptoms typically develop in adulthood. ARVC is present in 4% to 22% of athletes with sudden cardiac death, and there is some debate whether high-intensity endurance exercise may cause development of ARVC. ARVC is typically considered a disease of the desmosome, the structure that attaches heart muscle cells to one another. The desmosome provides strength to the muscle tissue and plays a role in signaling between neighboring cells. Variants in the genes associated with ARVC disrupt this function, causing detachment and death of myocardial cells when the heart muscle is under stress. Damaged myocardium is replaced with fat and scar tissue, eventually leading to structural and electrical abnormalities that can lead to arrhythmia. Inheritance of ARVC typically follows an autosomal dominant pattern of inheritance, and variants in DSC2, DSP, and PKP2 account for approximately half of the variants identified in ARVC. However, simultaneous testing of all known ARVC genes is recommended due to the potential for compound heterozygosity (biallelic variants on the same gene) or digenic heterozygosity (variants in 2 different genes). See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Arrhythmogenic Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, Neurogenic Scapuloperoneal Syndrome Kaezer Type, LGMD DSC2 Desmocollin AD, AR ARVC, ARVC + skin and hair findings DSG2 Desmoglein AD ARVC DSP Desmoplakin AD, AR ARVC, DCM, Carvajal syndrome JUP Junction plakoglobin AD, AR ARVC, Naxos disease LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy, ARVC (see OMIM for full listing) PKP2 Plakophilin 2 AD ARVC RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS TEMEM43 Transmembrane protein 43 AD ARVC, EMD TTN Titin AD, AR HCM, DCM, ARVC, myopathy Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), catecholaminergic polymorphic ventricular tachycardia (CPVT), long QT syndrome (LQTS), autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary arrhythmogenic right ventricular cardiomyopathy (ARVC or AC) Establishing a diagnosis of ARVC or AC, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
ARSAZ 35362

**ARSA Gene, Full Gene Analysis**

**Clinical Information:** Metachromatic leukodystrophy (MLD) is a rare autosomal recessive condition caused by mutations in the arylsulfatase A (ARSA) gene. The incidence of MLD is approximately 1:40,000 to 1:160,000, and the estimated carrier frequency in the general population is 1:100 to 1:200. MLD is characterized by the accumulation of cerebroside sulfate, which causes progressive demyelination and the loss of white matter. There is a variable age of onset. In the early onset form, symptoms appear in the first 1 to 2 years of life and include deterioration of skills such as walking and speaking. In the juvenile form, symptoms can appear between 4 years of age and the age of sexual maturity, and can include a decline in school performance and behavioral problems. Adults can present with a decline in school or job performance, substance abuse, and emotional lability. The diagnosis is suspected in individuals with progressive neurologic dysfunction and molecular resonance imaging evidence of leukodystrophy. The ARSA gene is located on chromosome 22 and has 8 exons. The following 4 mutations, c.459+1G>A, c.1204+1G>A, p.Pro426Leu, and p.Ile179Ser, account for 25% to 50% of mutations in the central and western European populations. The presence of 2 of these mutations within the ARSA gene confirms a diagnosis of metachromatic leukodystrophy. The recommended first-tier tests to screen for MLD are biochemical tests that measure arylsulfatase A enzyme activity in leukocytes and urine: ARSAW / Arylsulfatase A, Leukocytes and ARSU / Arylsulfatase A, 24 Hour, Urine. Individuals with decreased enzyme activity are more likely to have 2 mutations in the ARSA gene identifiable by molecular gene testing. However, arylsulfatase A enzyme assays cannot distinguish between MLD and ARSA pseudodeficiency, a clinically benign condition that leads to low in vitro ARSA levels, but it is found in 5% to 20% of the normal population. Thus, the diagnosis of MLD must be confirmed by molecular analysis of the ARSA gene.

**Useful For:** Second-tier test for confirming a diagnosis of metachromatic leukodystrophy (MLD) based on clinical findings and low ARSA activity levels Carrier testing when there is a family history of MLD, but disease-causing mutations have not been previously identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical Information:** Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic forms are the inorganic species of As(+3) (As-III), As(+5) (As-V), and their partially detoxified metabolites, monomethylarsine and dimethylarsine. As-III is more toxic than As-V and both are more toxic than mono- and dimethylarsine. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As-III-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats such as chicken that have been fed on seafood remnants may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid renal clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours.

**Useful For:** Diagnosis of arsenic intoxication

**Interpretation:** The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations ≥ 25 mcg inorganic arsenic per specimen are considered toxic. There is no limit to the normal range for the organic forms of arsenic, since they are not toxic and normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hours is >95% is present as the organic species from a dietary source, and <5% present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in food. A normal value for blood arsenic does not exclude a finding of an elevated urine inorganic arsenic, due to the very short half-life of blood arsenic.

**Reference Values:**

INORGANIC ARSENIC

0-24 mcg/specimen

Reference values apply to all ages.


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**Arsenic Fractionation, Random, Urine**

**Clinical Information:** Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic forms are the inorganic species of As(+3) (As-III), As(+5) (As-V), and their partially detoxified metabolites, monomethylarsine, and dimethylarsine. As-III is more toxic than As-V and both are more toxic than mono- and dimethylarsine. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As-III-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats such as chicken that have been fed on seafood remnants may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid renal clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours.
Useful For: Diagnosis of arsenic intoxication

Interpretation: The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations \( \geq 25 \text{ mcg} \) inorganic arsenic per specimen are considered toxic. There is no limit to the normal range for the organic forms of arsenic, since they are not toxic and normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hours is >95% is present as the organic species from a dietary source, and <5% present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in food. A normal value for blood arsenic does not exclude a finding of an elevated urine inorganic arsenic, due to the very short half-life of blood arsenic.

Reference Values:

INORGANIC ARSENIC

\( 0-24 \text{ mcg/L} \)

Reference values apply to all ages.


Arsenic, 24 Hour, Urine

Clinical Information: Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still 1 of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFR / Arsenic Fractionation, 24 Hour, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure.

Useful For: Preferred screening test for detection of arsenic exposure

Interpretation: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is <25 mcg/specimen. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), the urine output of arsenic may increase to 300 mcg/specimen for 1 day, after which it will decline to <25 mcg/specimen. Exposure to inorganic arsenic, the toxic form of
arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates >1,000 mcg/specimen indicate significant exposure. The highest level observed at Mayo Clinic was 450,000 mcg/specimen in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.

Reference Values:
0-35 mcg/specimen
Reference values apply to all ages.


Arsenic, Blood

Clinical Information: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(+5), also denoted as As(V), the more toxic As(+3), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(+3) is oxidized to As(+5) and then methylated to MMA and DMA. As a result of these detoxification steps, As(+3) and As(+5) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because of its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur.

Useful For: Detection of acute or very recent arsenic exposure Monitoring the effectiveness of therapy

Interpretation: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of <6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen.

Reference Values:
0-12 ng/mL
Reference values apply to all ages.


Arsenic, Hair

Clinical Information: Arsenic circulating in the blood will bind to protein by formation of a covalent
complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, "trapping" the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hair are used to document long-term (6 months-1 year) exposure.

**Useful For:** Detection of nonacute arsenic exposure

**Interpretation:** Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc. Hair arsenic >1.00 mcg/g dry weight indicates excessive exposure. It is normal for some arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death.

**Reference Values:**
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of hair

**Clinical References:**

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**Arsenic, Nails**

**Clinical Information:** Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mees' lines, may appear in the fingernails.

**Useful For:** Detection of nonacute arsenic exposure

**Interpretation:** Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. Nail arsenic >1.00 mcg/g dry weight indicates excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death.

**Reference Values:**
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of nails

**Clinical References:**

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**Arsenic, Random, Urine**

**Clinical Information:** Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still 1 of the more common toxicants found in...
insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3
different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to
dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the
conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of
energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely
on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results
in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine
triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the
lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells.
Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a
common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl
group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity.
Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the
small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion
in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a
known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and
symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea,
abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic
poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and
central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and
paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms
are nontoxic, inorganic forms are toxic. See ASFRU / Arsenic Fractionation, Random, Urine for details
about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for
arsenic in urine is the best screening test to detect arsenic exposure.

**Useful For:** Preferred screening test for detection of arsenic exposure

**Interpretation:** Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal
diet; therefore, normal urine arsenic output is <25 mcg/24 hours. After a seafood meal (seafood contains a
nontoxic, organic form of arsenic), the urine output of arsenic may increase to 300 mcg/24 hours for 1
day, after which it will decline to <25 mcg/24 hours. Exposure to inorganic arsenic, the toxic form of
arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates >50
mcg/L are a level of concern and >1,000 mcg/L indicates significant exposure. The highest level observed
at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow
breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of
peripheral neuropathy.

**Reference Values:**
0-35 mcg/L
Reference values apply to all ages.

**Clinical References:** 1. Fillol CC, Dor F, Labat L, et al: Urinary arsenic concentrations and
speciation in residents living in an area with naturally contaminated soils. Sci Total Environ 2010 Feb
Epidemiol 2009 Jan;19(1):59-68

**Arsenic/Creatinine Ratio, Random, Urine**

**Clinical Information:** Arsenic is perhaps the best known of the metal toxins, having gained notoriety
from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote
against acute arsenic poisoning. Even today, arsenic is still 1 of the more common toxicants found in
insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3
different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to
dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the
conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of
energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely
on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results
in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFRU / Arsenic Fractionation, Random, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure.

Useful For: Preferred screening test for detection of arsenic exposure

Interpretation: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is <35 mcg arsenic per gram creatinine (≤35 mcg/g). When exposed to inorganic arsenic, the urine output may be >1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be >200 mcg/g, after which it will decline to <35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates >1,000 mcg/g indicates significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.

Reference Values:

0-35 mcg/g Creatinine
Reference values apply to all ages.


Artichoke (Cynara scolymus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35

Arylsulfatase A, 24 Hour, Urine

Clinical Information: Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which leads to the accumulation of galactosyl sulfatide (cerebrosidase sulfate) in the white matter of the central nervous system and in the peripheral nervous system. Galactosyl sulfatide and, to a smaller extent, lactosyl sulfatide, also accumulate within
the kidney, gallbladder, and other visceral organs and are excreted in excessive amounts in the urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents between age 1 to 2 years with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs and most patients die within 5 years of the diagnosis. Juvenile MLD (20%-30% of cases) is characterized by onset between 4 to 14 years. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neuror degeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by mutations in the ARSA gene coding for the ARSA enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Extremely low ARSA levels have been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatide is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with a fairly common polymorphism in the ARSA gene which leads to low expression of the enzyme (5%-20% of normal). These patients can be difficult to differentiate from actual MLD patients. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis), urinary excretion of sulfatides (CTSA / Ceramide Trihexosides and Sulfatides, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures. Bone marrow transplantation remains controversial, and the effectiveness of enzyme replacement therapy may be limited due to difficulties crossing the blood-brain barrier. Other treatments under ongoing investigation include hematopoietic stem cell transplantation and fetal umbilical cord blood transplantation.

**Useful For:** Detection of metachromatic leukodystrophy

**Interpretation:** Greatly reduced levels of arylsulfatase A in urine (< or =15 nmol/h/mL), as well as in serum and various tissues, is seen in patients with metachromatic leukodystrophy. Individuals with pseudoaryl sulfatase A deficiency can have results in the affected range, but are otherwise unaffected with metachromatic leukodystrophy. Abnormal results should be confirmed using CTSA / Ceramide Trihexosides and Sulfatides, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis.

**Reference Values:**

> or =19 nmol/h/mL

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels.

Arylsulfatase A, Fibroblasts

Clinical Information: Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A enzyme, which leads to the accumulation of galactosyl sulfatide (cerebroside sulfate) in the white matter of the central nervous system and in the peripheral nervous system. Deficiency of the arylsulfatase A enzyme leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and visceral organs including the kidney and gallbladder. Patients with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, which are categorized based on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and typically presents between 6 months to 2 years of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs with most patients dying within 5 years of the diagnosis. Juvenile MLD (20%-30% of cases) is characterized by onset between 4 to 14 years. Typical presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by mutations in the ARSA gene coding for the arylsulfatase A enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency can have an identical clinical presentation to MLD but arylsulfatase A enzyme level is normal; however, patients with saposin B deficiency also excrete excessive amounts of sulfatides in their urine. Extremely low arylsulfatase A levels have been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatide is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with fairly common polymorphisms in the ARSA gene, which leads to low expression of the enzyme (5%-20% of normal). These patients can be difficult to differentiate from actual MLD patients. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis), urinary excretion of sulfatides (CTSA / Ceramide Trihexosides and Sulfatides, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures. Bone marrow transplantation remains controversial, and the effectiveness of enzyme replacement therapy may be limited due to difficulties crossing the blood-brain barrier. Other treatments under ongoing investigation include hematopoietic stem cell transplantation and fetal umbilical cord blood transplantation.

Useful For: Detection of metachromatic leukodystrophy

Interpretation: Arylsulfatase A is deficient in metachromatic leukodystrophy and multiple sulfatase deficiency. Abnormal results should be confirmed using CTSA / Ceramide Trihexosides and Sulfatides, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis.

Reference Values:
> or =4.25 nmol/min/mg protein

Clinical Information: Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and to a lesser extent, in visceral organs including the kidney and gallbladder. Patients with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, which are categorized based on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents between 6 months to 2 years of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs with most patients dying within 5 years of the diagnosis. Juvenile MLD (20%-30% of cases) is characterized by onset between 4 to 14 years. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by mutations in the ARSA gene coding for the ARSA enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Extremely low ARSA levels have been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatide is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with fairly common polymorphisms in the ARSA gene, which leads to low expression of the enzyme (5%-20% of normal). These patients can be difficult to differentiate from actual MLD patients. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis), urinary excretion of sulfatides (CTSA / Ceramide Trihexosides and Sulfatides, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures. Bone marrow transplantation remains controversial, and the effectiveness of enzyme replacement therapy may be limited due to difficulties crossing the blood-brain barrier. Other treatments under ongoing investigation include hematopoietic stem cell transplantation and fetal umbilical cord blood transplantation.

Useful For: Preferred test for detection of metachromatic leukodystrophy

Interpretation: Decreased enzyme levels indicate an individual is affected with metachromatic leukodystrophy (MLD). Note that individuals with pseudoaryl-sulfatase A deficiency can have results in this range, but are otherwise unaffected with MLD. Abnormal results should be confirmed using CTSA / Ceramide Trihexosides and Sulfatides, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis.

Reference Values:
> or =62 nmol/h/mg

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels. Low normal values may be due to the presence of pseudodeficiency gene or carrier gene. Patients with these depressed levels may be phenotypically normal.

Arylsulfatase B, Fibroblasts

Clinical Information: Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of N-acetylgalactosamine 4-sulfatase, also known as arylsulfatase B (ARSB). The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of complex macromolecules called glycosaminoglycans (GAGs) including dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate. Accumulation of GAGs (also called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, hepatosplenomegaly, corneal clouding, and cardiac disease. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAGs, and can lead to death before the second or third decades. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAGs, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. A diagnostic workup in an individual with MPS VI typically demonstrates elevated levels of urinary GAGs and increased dermatan sulfate detected on thin-layer chromatography. Reduced or absent activity of ARSB in leukocytes and/or fibroblasts is suggestive of a diagnosis of MPS VI. Sequencing of the ARSB gene allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members (MPS6Z / Mucopolysaccharidosis VI, Full Gene Analysis). Currently, no clear genotype-phenotype correlations have been established. ARSB activity is also reduced in 2 other rare autosomal recessive disorders, multiple sulfatase deficiency (MSD) and mucolipidosis II (I-cell disease). Both of these conditions present with developmental delays that make them clinically different from MPS VI. The symptoms of MSD mimic metachromatic leukodystrophy (MLD) as well as the mucopolysaccharidoses and can include developmental delay, neurologic regression, dysmorphic facies, dysostosis multiplex, organomegaly, ichthyosis, and chondroplasia punctata. If MSD is suspected, testing of an additional sulfatase enzyme, such as arylsulfatase A in MLD, can help determine if multiple sulfatases are deficient. I-cell disease is characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. This is a progressive disorder and death typically occurs in the first decade of life. Additional testing including hydrolase enzymes in serum, such as hexosaminidase A in Tay-Sach disease, is recommended if a diagnosis of I-cell is suspected.

Useful For: Diagnosis of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)

Interpretation: Arylsulfatase B is deficient in mucopolysaccharidosis VI, multiple sulfatase deficiency, and mucolipidosis II.

Reference Values:
> or = 6.08 nmol/min/mg protein

Ascaris, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


Ascorbic Acid (Vitamin C), Plasma

**Clinical Information:** Ascorbic acid (vitamin C) is essential for the enzymatic amidation of neuropeptides, production of adrenal cortical steroid hormones, promotion of the conversion of tropocollagen to collagen, and metabolism of tyrosine and folate. It also plays a role in lipid and vitamin metabolism and is a powerful reducing agent or antioxidant. Specific actions include: activation of detoxifying enzymes in the liver, antioxidation, interception and destruction of free radicals, preservation and restoration of the antioxidant potential of vitamin E, and blockage of the formation of carcinogenic nitrosamines. In addition, vitamin C appears to function in a variety of other metabolic processes in which its role has not been well characterized. Prolonged deficiency of vitamin C leads to the development of scurvy, a disease characterized by an inability to form adequate intercellular substance in connective tissues. This results in the formation of swollen, ulcerative lesions in the gums, mouth, and other tissues.
that are structurally weakened. Early symptoms may include weakness, easy fatigue and listlessness, as well as shortness of breath and aching joints, bones, and muscles. The need for vitamin C can be increased by the use of aspirin, oral contraceptives, tetracycline, and a variety of other medications. Psychological stress and advancing age also tend to increase the need for vitamin C. Among the elderly, lack of fresh fruit and vegetables often adds vitamin C depletion to the inherently increased need, with development of near-scurvy status.

**Useful For:** Diagnosing vitamin C deficiency As an aid to deter excessive intake

**Interpretation:** Values <0.3 mg/dL indicate significant deficiency. Values >0.6 mg/dL indicate adequate supply. The actual level at which vitamin C is excessive has not been defined. Values >3.0 mg/dL are suggestive of excess intake. Whether vitamin C in excess is indeed toxic continues to be uncertain. However, limited observations suggest that this condition may induce uricosuria and, in individuals with glucose-6-phosphate dehydrogenase deficiency, may induce increased red blood cell fragility.

**Reference Values:**
0.6-2.0 mg/dL


**Ashkenazi Jewish Mutation Analysis Panel Without Cystic Fibrosis (CF)**

**Clinical Information:** Certain genetic diseases are more common in individuals of Ashkenazi Jewish heritage (Jewish individuals of Eastern European ancestry) compared to the non-Jewish population. The majority of these conditions are inherited in an autosomal recessive manner. This group of diseases includes Gaucher, Tay-Sachs, familial dysautonomia, Canavan, mucolipidosis IV, Niemann-Pick Type A and B, FANCC-related Fanconi anemia, and Bloom syndrome. While these conditions are observed outside of the Ashkenazi Jewish population, they occur at a lower frequency. It is estimated that an individual of Ashkenazi Jewish ancestry has a 20% to 25% chance of being a carrier of 1 of these diseases. Gaucher Disease: Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Mutations in the beta-glucocerebrosidase gene, GBA, cause the clinical manifestations of Gaucher disease. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. Type 1 disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. There is a broad spectrum of disease in type 1, with some patients exhibiting severe symptoms and others very mild disease. Types 2 and 3 are associated with neurological disease of variable onset and progression, though type 2 tends to be more severe. Eight common GBA mutations, including the N370S mutation most commonly found in the Ashkenazi Jewish population, are included in this test: delta55bp, V394L, N370S, IVS2+1G->A, 84G->GG, R496H, L444P, and D409H. Tay-Sachs: Tay-Sachs disease is caused by an absence of hexosaminidase (HexA) enzyme activity, which results in the accumulation of the sphingolipid GM2 ganglioside. Mutations in the HEXA gene cause the clinical manifestations of Tay-Sachs disease (TSD). The most common form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations of this condition include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. This panel tests for the 3 common mutations in the Ashkenazi Jewish population: 1278insTATC, G269S, and IVS12+1G->C. Also included in this assay are the mutations IVS9+1G->A and delta.7.6kb mutations along with the R247W and R249W polymorphisms associated with pseudodeficiency. Familial Dysautonomia: Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons. Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal...
degeneration continues throughout the lifespan. Mutations in the IKBKAP gene cause the clinical manifestations of familial dysautonomia. Two mutations in the IKBKAP gene are common in the Ashkenazi Jewish population: IVS20(+6)T→C and R696P. Canavan Disease: Canavan disease is a severe leukodystrophy resulting from a deficiency of the enzyme aspartoacylase. Mutations in the ASPA gene cause the clinical manifestations of Canavan disease. The deficiency of aspartoacylase leads to spongy degeneration of the brain, and the disease is characterized by delayed development beginning at age 3 to 6 months, head lag, macrocephaly, and hypotonia. Death usually occurs in the first decade of life. Four ASPA mutations are included in this test: 433(-2)A→G, A305E, E285A, and Y231X. Mucolipidosis IV: Mucolipidosis IV is a lysosomal storage disease characterized by mental retardation, hypotonia, corneal clouding, and retinal degeneration. Mutations in the MCOLN1 gene are responsible for the clinical manifestations of mucolipidosis IV. Two mutations in the MCOLN1 gene account for the majority of mutations in the Ashkenazi Jewish population: IVS3(-2)A→G and delta6.4kb. Niemann-Pick Disease Types A and B: Niemann-Pick disease (types A and B) is a lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is milder, though variable in its clinical presentation. Most individuals with type B do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are known to cause Niemann-Pick disease types A and B. There are 3 common mutations causing Niemann-Pick type A in the Ashkenazi Jewish population: L302P, R496L, and fsP330. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutation alleles in Gran Canaria Island. Fanconi Anemia: Fanconi anemia is an aplastic anemia that leads to bone marrow failure and myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, IVS4(+4)A→T, in the FANCC gene is common in the Ashkenazi Jewish population. A second mutation, 322delG, is overrepresented in FANCC patients of Northern European ancestry. Bloom Syndrome: Bloom syndrome is characterized by short stature, sun sensitivity, susceptibility to infections, and a predisposition to cancer. Mutations in the BLM gene lead to genetic instability (increased chromosomal breakage and sister chromatid exchange) and cause the clinical manifestations of Bloom syndrome. The protein encoded by the BLM gene is a helicase involved in maintaining DNA integrity. There is a common mutation in the Ashkenazi Jewish population: 2281delATCTGAinsTAGATTC (2281del6/ins7). Because of the high sensitivity of carrier testing in the Ashkenazi Jewish population, the American College of Medical Genetics and Genomics (ACMG) recommends that carrier screening for cystic fibrosis, Canavan, Tay-Sachs, familial dysautonomia, Niemann-Pick type A, Fanconi anemia (FANCC), Bloom syndrome, mucolipidosis IV, and Gaucher disease be offered to individuals of Ashkenazi Jewish ancestry. The mutation detection rates and carrier frequencies for the diseases included in this panel are listed below. Of note, testing for cystic fibrosis is not included in this panel. If testing for this disorder is desired, please see details and ordering information under CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel. Disease Carrier Rate in the AJ Population Mutation Detection Rate Gaucher 1/18 95% Tay-Sachs 1/31 *99% Familial dysautonomia 1/31 99% Canavan 1/41 98% Mucolipidosis IV 1/127 95% Niemann-Pick type A/B 1/90 97% FANCC-related Fanconi anemia 1/89 >99% Bloom syndrome 1/107 >99% *with biochemical testing The Ashkenazi Jewish panel is useful for identifying carriers of these 8 conditions in an at-risk population. Because the diseases included in the panel are inherited in an autosomal recessive manner, the presence of a family history is not a prerequisite for testing consideration. The identification of disease-causing mutations allows for carrier testing of at-risk family members and prenatal diagnosis for pregnancies in which both parents are known carriers. Refer to Carrier Testing for Tay-Sachs Disease and Other GM2 Gangliosidosis Variants: Supplementing Traditional Biochemical Testing with Molecular Methods, Mayo Medical Laboratories Communique 2004 Jul;29(7) for more information regarding diagnostic strategy. Of note, approximately 1 in 25 individuals of Ashkenazi Jewish ancestry are also carriers of cystic fibrosis (CF). Therefore, the American College of Medical Genetics also recommends that carrier screening for CF be offered to individuals of Ashkenazi Jewish ancestry who are pregnant or considering pregnancy. Carrier screening for CF is available by ordering CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel.

**Useful For:** Carrier screening in individuals of Ashkenazi Jewish ancestry for Bloom syndrome, Canavan disease, FANCC-related Fanconi anemia, familial dysautonomia, Gaucher disease, mucolipidosis IV, Niemann-Pick disease types A and B, and Tay-Sachs disease
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** Gross SJ, Pletcher BA, Monaghan KG: Carrier screening individuals of Ashkenazi Jewish descent. Genet Med 2008;10(1):54-56

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**Asparagin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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</tr>
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<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

involving mild tissue injury, the predominant form of AST is that from the cytoplasm. Severe tissue
damage results in more of the mitochondrial enzyme being released. High levels of AST can be found in
cases such as myocardial infarction, acute liver cell damage, viral hepatitis and carbon tetrachloride
poisoning. Slight to moderate elevation of AST is seen in muscular dystrophy, dermatomyositis, acute
pancreatitis and crushed muscle injuries.

Useful For: Diagnosing and monitoring liver disease, particularly diseases resulting in a destruction of
hepatocytes

Interpretation: Elevated aspartate aminotransferase (AST) values are seen in parenchymal liver
diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the
normal range. Levels may reach values as high as one hundred times the upper reference limit, although
twenty to fifty-fold elevations are most frequently encountered. In infectious hepatitis and other
inflammatory conditions affecting the liver, alanine aminotransferase (ALT) is characteristically as high
as or higher than AST, and the ALT/AST ratio, which normally and in other condition is <1, becomes
greater than unity. AST levels are usually elevated before clinical signs and symptoms of disease appear.
Five- to 10-fold elevations of both AST and ALT occur in patients with primary or metastatic carcinoma
of the liver, with AST usually being higher than ALT, but levels are often normal in the early stages of
malignant infiltration of the liver. Elevations of ALT activity persist longer than do those of AST activity.
Elevated AST values may also be seen in disorders affecting the heart, skeletal muscle and kidney.

Reference Values:
Males
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L
Females
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L


FASPE
57947

Aspen (Populus tremuloides) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2
0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“

Reference Values:
<0.35 kU/L

ASPAG
84356

Aspergillus (Galactomannan) Antigen, Serum

Clinical Information: Invasive aspergillosis (IA) is a severe infection that occurs in patients with
prolonged neutropenia, following transplantation or in conjunction with aggressive immunosuppressive
regimens (eg, prolonged corticosteroid usage, chemotherapy). The incidence of IA is reported to vary
from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to
80% due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death).
Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA
requires histopathological evidence of deep-tissue invasion or a positive culture. However, this evidence
is often difficult to obtain due to the critically ill nature of the patient and the fact that severe
thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The
sensitivity of culture in this setting also is low, reportedly ranging from 30% to 60% for bronchoalveolar
lavage fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained
fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography [CT]
scan); and definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the Food and Drug Administration for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of galactomannan can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs.

**Useful For:** An aid in the diagnosis of invasive aspergillosis and assessing response to therapy

**Interpretation:** A positive result supports a diagnosis of invasive aspergillosis (IA). Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence. See Cautions. A negative result does not rule out the diagnosis of IA. Repeat testing is recommended if the result is negative but IA is suspected. Patients at risk of IA should have a baseline serum tested and should be monitored twice a week for increasing galactomannan antigen levels. Galactomannan antigen levels may be useful in the assessment of therapeutic response. Antigen levels decline in response to antimicrobial therapy.

**Reference Values:**
<0.5 index

**Clinical References:**

**FASP**
91607

**Aspergillus Antibodies, Immunodiffusion, Serum**

**Reference Values:**
Aspergillus flavus Ab
Aspergillus niger Ab
Aspergillus fumigatus Ab

Reference Range: Negative

Interpretive Criteria:
- Negative: Antibody not detected
- Positive: Antibody detected

A positive result is represented by 1 or more precipitin bands, and may indicate fungus ball, allergic bronchopulmonary aspergillosis (ABA) or invasive aspergillosis. Generally, the appearance of 3 â€“ 4 bands indicates either fungus ball or ABA.

**ASPBA**
61009

**Aspergillus Antigen, Bronchoalveolar Lavage**

**Clinical Information:** Invasive aspergillosis (IA) is a severe infection that occurs in patients with prolonged neutropenia following transplantation or in conjunction with aggressive immunosuppressive regimens (eg, prolonged corticosteroid use, chemotherapy). The incidence of IA is reported to vary from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to 80%, due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death). Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA requires
histopathological evidence of deep-tissue invasion or a positive culture. However, this evidence is often difficult to obtain due to the critically ill nature of the patient and the fact that severe thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The sensitivity of culture in this setting also is low, reportedly ranging from 30% to 60% for bronchoalveolar lavage (BAL) fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography [CT] scan), and a definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the FDA for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan (Aspergillus antigen) can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of Aspergillus antigen can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs. The clinical utility of Aspergillus antigen testing in BAL specimens as an early prognostic indicator of IA has recently been assessed. These studies demonstrated equivalent or higher sensitivity compared to detection of Aspergillus antigen in serum. (1-4) This assay may be useful in the assessment of therapeutic response as antigen levels typically decline in response to effective antimicrobial therapy.

**Useful For:** As an aid in the diagnosis of invasive aspergillosis and assessing response to therapy

**Interpretation:** A positive result in bronchoalveolar lavage (BAL) fluid supports a diagnosis of invasive, pulmonary aspergillosis. Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence (see Cautions). A negative result in BAL fluid does not rule out the diagnosis of invasive aspergillosis (IA). Patients at risk of IA should be monitored twice a week for Aspergillus antigen levels in serum until determined to be clinically unnecessary. Aspergillus antigen levels typically decline in response to effective antimicrobial therapy.

**Reference Values:**

<0.5 Index

**Clinical References:**


**Aspergillus flavus IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Aspergillus fumigatus, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergens. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Aspergillus fumigatus, IgG Antibodies, Serum**

**Clinical Information:** Aspergillus fumigatus is one of the causative agents of hypersensitivity pneumonitis (HP), as well as invasive lung disease with cavitation or pneumonitis and allergic bronchopulmonary disease.(1) Other causative microorganisms of HP include Micropolyspora faeni and Thermoactinomyces vulgaris. The development of HP and allergic bronchopulmonary disease caused by Aspergillus fumigatus is accompanied by an immune response to Aspergillus fumigatus antigens with production of IgG or IgE antibodies, respectively. While the immunopathogenesis of HP and allergic bronchopulmonary disease is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.

**Useful For:** Evaluation of patients suspected of having lung disease caused by Aspergillus fumigatus

**Interpretation:** Elevated concentrations of IgG antibodies to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**

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SASP

9678
<4 years: not established  
> or =4 years: < or =102 mg/L


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**FAGPP 57903**  
**Aspergillus IgG Precipitins Panel**

**Interpretation:** The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

**Reference Values:**
Negative

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**ASPG 86324**  
**Aspergillus niger, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
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ADMA 83651

Asymmetric Dimethylarginine, Plasma

**Clinical Information:** Asymmetric dimethylarginine (ADMA) is an independent risk factor for coronary heart disease. ADMA inhibits nitric oxide (NO) synthesis and is elevated in diseases related to endothelial dysfunction including hypertension, hyperlipidemia, and type-II diabetes mellitus. Elevation in ADMA and subsequent NO synthesis inhibition leads to vasoconstriction, reduced peripheral blood flow, and reduced cardiac output. Elevated plasma ADMA confers a 4- to 6-fold increased risk of subsequent cardiovascular events or mortality among patients with acute coronary syndrome (2), unstable angina (3), type-II diabetes mellitus (4), end-stage renal disease (5), and coronary heart disease (6). Among patients with coronary heart disease, baseline ADMA remained a significant risk factor of adverse events even after adjusting for LDL-C, HDL-C, triglycerides, creatinine and high sensitivity C-reactive protein. Plasma ADMA concentrations are lowered by rosuvastatin and atorvastatin, but not simvastatin in patients with hypercholesterolemia. Addition of vildagliptin (Galvus) to metformin significantly reduced ADMA concentrations among patients with type-II diabetes mellitus (8).

**Useful For:** An adjunct to other risk markers for assessing an individual's likelihood of future coronary events, in patients with coronary heart disease, type-II diabetes mellitus, or kidney disease

**Interpretation:** In patients with pre-existing coronary conditions or at high risk for coronary events (diabetes, renal insufficiency), asymmetric dimethylarginine (ADMA) levels in the upper tertile, >112 ng/mL, confer an increased risk for future coronary events. Reductions in ADMA are not known to be predictive of decreased risk of future coronary effects.

**Reference Values:**
- <18 years: not established
- > or =18 years: 63-137 ng/mL

**Clinical References:**
Atypical Hemolytic Uremic Syndrome (aHUS) Complement Interpretation

Reference Values:
Only orderable as part of a profile. For more information see AHUSC / Atypical Hemolytic Uremic Syndrome (aHUS) Complement Panel, Serum and Plasma.

Clinical Information: Individuals presenting with thrombotic microangiopathies (TMAs) require clinical testing to identify the underlying cause. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are both acute syndromes with many overlapping clinical features. Reduced levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motives) activity is associated with TTP and is one laboratory feature that distinguishes TTP from HUS. HUS can also have a number of causes; one of the rarer forms of disease is caused by defects in the alternative pathway of the complement system, so called atypical-HUS (aHUS). Patients with defective alternative pathway regulation can benefit from biologics that suppress the complement system. The purpose of this panel is to aid in the differential diagnosis of TMAs. The suggested approach is to rule out other causes of TMAs first, since aHUS is one of the rarer causes of TMAs.

Useful For: Detecting deficiencies in the alternative pathway that can cause atypical-hemolytic uremic syndrome, dense deposit disease, and C3 glomerulonephritis

Interpretation: An interpretive report will be included.

Reference Values:
FACTOR B COMPLEMENT ANTIGEN
15.2-42.3 mg/dL

SC5b-9 COMPLEMENT
< or =250 ng/mL normal

FACTOR H COMPLEMENT ANTIGEN
23.6-43.1 mg/dL

C4d COMPLEMENT ACTIVATION FRAGMENT
< or =9.8 mcg/mL

CBb COMPLEMENT ACTIVATION FRAGMENT
< or =1.6 mcg/mL

COMPLEMENT C4
14-40 mg/dL

COMPLEMENT C3
75-175 mg/dL

COMPLEMENT, ALTERNATE PATHWAY (AH50), FUNCTIONAL
> or =46% normal
COMPLEMENT, TOTAL
> or =16 years: 30-75 U/mL
Reference values have not been established for patients who are <16 years of age.


**FAPPN**

Atypical Pneumonia DNA Panel Qual
Reference Values:
Reference Range: Not detected

**FAPPL**

Atypical Pneumonia Panel
Reference Values:
Chlamydia and Chlamydophila Antibody Panel 3 (IgG, IgA, IgM)
C.Trachomatis, C.Pneumoniae, C.Psittaci  (IgG, IgA, IgM )
Reference Range:  IgG < 1:64
        IgA < 1:16
        IgM < 1:10

The immunofluorescent detection of specific antibodies to Chlamydia trachomatis, Chlamydophila pneumoniae, and C. psittaci may be complicated by crossreactive antibodies, non-specific antibody stimulation, or past exposure to more than one of these organisms. IgM titers of 1:10 or greater are indicative of recent infection; however, IgM antibody is very crossreactive, often demonstrating titers to multiple organisms. Any IgG titer may indicate past exposure to that particular organism. Infection by a particular organism typically yields IgG titers that are higher than antibody titers to non-infecting organisms. IgA titers may help to identify the infecting organism when crossreactive IgG is present. IgA is typically present at low titers during primary infection, but may be elevated in recurrent exposures or in chronic infection.

Legionella Pneumophila Antibodies (Total)
L. pneumophila (serogroup 1) and (serogroups 2-6, 8)
Reference Ranges:  <1:16

Total antibodies to Legionella pneumophila serogroup 1 and 6 additional L. pneumophila serogroups (2, 3, 4, 5, 6, 8) are measured using a polyvalent conjugate.

The antibody response to Legionella may be detected 4 days to 6 weeks after exposure and may remain elevated for months or years. Thus, a fourfold or greater rise in titer is required to confirm a diagnosis of current infection. Serologic testing does not usually allow definitive differentiation of Legionella serogroups.

Mycoplasma Pneumoniae Antibody (IgG)
Reference Range:  <=0.90

Interpretive criteria;
<=0.90  Negative
0.91-1.09  Equivocal
A positive result indicates that the patient has antibody to Mycoplasma. It does not differentiate between an active or past infection. The clinical diagnosis must be interpreted in conjunction with the clinical signs and symptoms of the patient.

Mycoplasma Pneumoniae Antibody (IgM)

Reference Range: <770 U/mL

Interpretive criteria:

- <770 U/mL  Negative
- 770-950 U/mL  Low positive
- >950 U/mL  Positive

Aureobasidium pullulans, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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**Australian Pine, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>
| 6     | > or =100| Strongly positive Reference values apply to all ages.


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**Autoimmune Dysautonomia Evaluation, Serum**

**Clinical Information:** Autoimmune dysautonomia encompasses disorders of peripheral autonomic synapses, ganglionic neurons, autonomic nerve fibers, and central autonomic pathways mediated by neural-specific IgG or effector T cells. These disorders may be idiopathic or paraneoplastic, subacute or insidious in onset, and may present as a limited disorder or generalized pandysautonomia. Pandysautonomia is usually subacute in onset and severe, and includes impaired pupillary light reflex, anhidrosis, orthostatic hypotension, cardiac arrhythmias, gastrointestinal dysmotility, sicca manifestations, and bladder dysfunction. Limited dysautonomia is confined to 1 or just a few domains, is often mild and may include sicca manifestations, postural orthostatism and cardiac arrhythmias, bladder...
dysfunction or gastrointestinal dysmotilities. Diagnosis of limited dysautonomia requires documentation of objective abnormalities by autonomic reflex testing, thermoregulatory sweat test, or gastrointestinal motility studies. The most commonly encountered autoantibody marker of autoimmune dysautonomia is the neuronal ganglionic alpha-3- (acetylcholine receptor: AChR) autoantibody. This autoantibody to date is the only proven effector of autoimmune dysautonomia. A direct relationship has been demonstrated between antibody titer and severity of dysautonomia in both alpha-3-AChR-immunized animals and patients with autoimmune dysautonomia. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally have profound pandysautonomia. Dysautonomic patients with lower alpha-3-AChR autoantibody values (0.03-0.99 nmol/L) have limited dysautonomia. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancers recognized most commonly include small-cell lung carcinomas, thymoma, adenocarcinomas of breast, lung, prostate, and gastrointestinal tract, and lymphoma. Cancer risk factors include a past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors neurologic improvement and lessens morbidity. Autoantibodies to other onconeural proteins shared by neurons, glia or muscle (eg, antineuronal nuclear antibody-type 1: ANNA-1, CRMP-5-IgG, N-type voltage-gated calcium channel, muscle AChR and sarcomeric [striational antigens]) serve as additional markers of paraneoplastic or idiopathic dysautonomia. A specific neoplasm is often predictable by the individual patient's autoimmune antibody profile.

**Useful For:** Investigating idiopathic dysautonomic symptoms Directing a focused search for cancer in patients with idiopathic dysautonomia Investigating autonomic symptoms that appear in the course or wake of cancer therapy, and are not explainable by recurrent cancer or metastasis (detection of autoantibodies in this profile helps differentiate autoimmune dysautonomia from the effects of chemotherapy)

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and glia are valuable serological markers of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 autoantibody to be detected in patients with autoimmune dysautonomia. These include: - Plasma membrane cation channel antibodies (neuronal ganglionic [alpha-3] and muscle [alpha-1] acetylcholine receptor; neuronal calcium channel N-type or P/Q-type, and neuronal voltage-gated potassium channel antibodies). All of these autoantibodies are potential effectors of autonomic dysfunction. - Antineuronal nuclear autoantibody-type 1 - Neuronal and muscle cytoplasmic antibodies (CRMP-5 IgG, glutamic acid decarboxylase and striational) A rising autoantibody titer in previously seropositive patients suggests cancer recurrence.

**Reference Values:**

**CATION CHANNEL ANTIBODIES**
- N-Type Calcium Channel Antibody
  - ≤0.03 nmol/L
- P/Q-Type Calcium Channel Antibody
  - ≤0.02 nmol/L
- AChR Ganglionic Neuronal Antibody
  - ≤0.02 nmol/L
- Neuronal VGKCs Autoantibody
  - ≤0.02 nmol/L
- Glutamic Acid Decarboxylase (GAD65) Antibody
  - ≤0.02 nmol/L

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1)
  - <1:240
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2)
  - <1:240
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3)
  - <1:240
- Anti-Gliarial/Neuronal Nuclear Antibody-Type 1 (AGNA-1)
  - <1:240

Current as of July 8, 2016 11:28 am CDT
NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES

Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) <1:240
Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) <1:240
Purkinje Cell Cytoplasmic Antibody, Type Tr (PCA-Tr) <1:240
Amphiphysin Antibody <1:240
CRMP-5-IgG <1:240
Note: Titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 or 507-266-5700 to request CRMP-5 Western blot.

Striational (Striated Muscle) Antibodies <1:120

ACHR RECEPTOR ANTIBODIES

ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L
AChR Receptor (Muscle) Modulating Antibody
0-20% loss of AChR

NEUROMYELITIS OPTICA (NMO)/AQUAPORIN-4-IGG CELL-BINDING ASSAY
Negative
Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative
N-Methyl-D-aspartate receptor (NMDA-R) CBA
Negative
IFA <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptor (AMPA-R) CBA
Negative
IFA <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R) CBA
Negative
IFA <1:120

studies (eg, gastric, small intestinal or colonic nuclear transit studies; esophageal, gastro-duodenal, or colonic manometry or anorectal manometry with balloon expulsion). These disorders target autonomic postganglionic synaptic membranes and in some cases ganglionic neurons and autonomic nerve fibers, and may be accompanied by sensory small fiber neuropathy. Onset may be subacute or insidious. There may be additional manifestations of dysautonomia (eg, impaired pupillary light reflex, anhidrosis, orthostatic hypotension, sicca manifestations, and bladder dysfunction) or signs of other neurologic impairment. Autonomic reflex testing and a thermoregulatory sweat test are valuable aids in documentation of objective abnormalities. The serological profile of AGID may include autoantibodies specific for onconeural proteins found in the nucleus, cytoplasm, or plasma membrane of neurons or muscle. Some of these autoantibodies are highly predictive of an underlying cancer. A commonly encountered autoantibody marker of AGID is the ganglionic neuronal alpha-3-AChR (acetylcholine receptor) autoantibody. The pathogenicity of this autoantibody was demonstrated in rabbits immunized with a recombinant extracellular fragment of the alpha-3-AChR subunit, and in mice injected with IgG from high-titered alpha-3-AChR autoantibody-positive rabbit or human sera. A direct relationship between antibody titer and severity of dysautonomia occurs in both experimental animals and patients. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally present with profound pandysautonomia, and those with lower alpha-3-AChR autoantibody values may have limited autoimmune dysautonomia, or other neurological symptoms and signs. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancer risk factors include the patient's past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors less morbidity from the GI dysmotility disorder. The cancers recognized most commonly with alpha-3-AChR autoantibody include adenocarcinomas of breast, lung, prostate, and GI tract, or lymphoma. A specific neoplasm is often predictable when a patient's autoantibody profile includes other autoantibodies to onconeural proteins shared by neurons, glia, or muscle. Small-cell lung carcinoma is found in 80% of antineuronal nuclear antibody-type 1 (ANNA-1) (anti-Hu)-positive patients and 23% of ANNA-1-positive patients have GI dysmotility. The most common GI manifestation is gastroparesis, but the most dramatic is pseudo-obstruction.

**Useful For:** Investigating unexplained weight loss, early satiety, anorexia, nausea, vomiting, constipation or diarrhea in a patient with past or family history of cancer or autoimmunity Directing a focused search for cancer Investigating gastrointestinal symptoms that appear in the course or wake of cancer therapy, not explainable by recurrent cancer, metastasis or therapy; detection of autoantibodies on this profile helps differentiate autoimmune gastrointestinal dysmotility from the effects of chemotherapy Detecting early evidence of cancer recurrence in previously seropositive patients who have a rising titer of 1 or more autoantibodies

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute symptoms and signs. It is not uncommon for more than 1 antibody to be detected. Three classes of antibodies are recognized (the individual antibodies from each class included in the profile are denoted in parentheses): -Antineuronal nuclear autoantibody-type 1 -Neuronal and muscle cytoplasmic (CRMP-5, glutamic acid decarboxylase, and striational) -Plasma membrane cation channel (neuronal ganglionic [alpha-3-AChR (acetylcholine receptor)] and muscle AChR, neuronal voltage-gated N-type calcium channel, neuronal voltage-gated potassium channel antibodies). All of these autoantibodies are potential effectors of autoimmune gastrointestinal dysmotility.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**

Antineuronal Nuclear Ab, Type 1 (ANNA-1) <1:240
Antineuronal Nuclear Ab, Type 2 (ANNA-2) <1:240
Antineuronal Nuclear Ab, Type 3 (ANNA-3) <1:240
Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
Purkinje Cell Cytoplasmic Ab, Type 1 (PCA-1) <1:240
Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2) <1:240
Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr) <1:240
Amphiphysin Antibody <1:240
CRMP-5-IgG <1:240
Striational (Striated Muscle) Antibodies <1:120

WESTERN BLOT
Paraneoplastic Western Blot Negative
CRMP-5-IgG Western Blot Negative
Amphiphysin Western Blot Negative

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody < or =0.02 nmol/L

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody < or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody < or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody < or =0.02 nmol/L
Neuronal VGKC Autoantibody < or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACh Receptor (Muscle) Binding Antibody < or =0.02 nmol/L
AChR Receptor (Muscle) Modulating Antibody
0-20% loss of AChR
N-Methyl-D-aspartate receptor (NMDA-R) CBA Negative
IFA: <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R) CBA Negative
IFA: <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R) CBA Negative
IFA: <1:120
NMO/AQP4-IgG Negative


**Autoimmune Liver Disease Panel, Serum**

**Clinical Information:** Autoimmune liver diseases result from damage to hepatocytes or cholangiocytes caused by an inflammatory immune reaction. Included within this disease group are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). In some cases, patients with these diseases may present asymptotically, with increases in various liver enzymes being identified incidentally during an unrelated clinical evaluation. On the other end of the spectrum are patients who present with clinical evidence of liver disease, including fatigue, hepatomegaly, ascites, esophageal varices, and/or jaundice. Diagnosis of an autoimmune liver disease first requires that other etiologies of liver injury, including viral, hepatic, drug, and metabolic causes, be excluded. In some situations, a liver biopsy may be indicated. For those patients in whom an autoimmune liver disease is suspected, autoantibody serology testing may be considered. The Autoimmune Liver Disease Panel includes markers that may support a diagnosis of an autoimmune liver disease, specifically AIH or PBC. Unfortunately, there are no known autoantibodies specific for PSC that are useful as diagnostic markers. Patients with AIH may be positive for smooth muscle antibodies (SMAs) and/or antinuclear antibodies (ANAs). The SMAs associated with AIH are generally specific for F-actin. SMAs have a specificity of 80% to 90% for AIH, although the sensitivity is only in the range of 70% to 80%. In contrast, ANAs, although relatively sensitive for AIH, lack specificity, being associated with a variety of autoimmune diseases. Both SMA and ANA, along with other lab markers and biopsy evaluation, are included in the international diagnostic criteria for AIH. Anti-mitochondrial antibodies (AMAs) are a diagnostic marker for PBC. AMAs are found in >90% of patients with PBC, with a specificity of >95%. AMAs are included in the diagnostic criteria for PBC, which was developed through an international collaborative effort.

**Useful For:** Evaluation of patients with suspected autoimmune liver disease, specifically autoimmune hepatitis or primary biliary cirrhosis. Evaluation of patients with liver disease of unknown etiology.

**Interpretation:** The presence of smooth muscle antibodies (SMAs) and/or antinuclear antibodies (ANAs) is consistent with a diagnosis of chronic autoimmune hepatitis, in patients with clinical and/or laboratory evidence of hepatocellular damage. The presence of anti-mitochondrial antibodies (AMAs) is consistent with a diagnosis of primary biliary cirrhosis, in patients with clinical and/or laboratory evidence of hepatobiary damage.

**Reference Values:**

**SMOOTH MUSCLE ANTIBODIES**
- Negative
- If positive, results are titered.
- Reference values apply to all ages

**MITOCHONDRIAL ANTIBODIES (M2)**
- Negative: <0.1 Units
- Borderline: 0.1-0.3 Units
- Weakly positive: 0.4-0.9 Units
- Positive: > or =1.0 Units
- Reference values apply to all ages

**ANTINUCLEAR ANTIBODIES (ANA2)**
- Negative: < or =1.0 Units
- Weakly positive: 1.1-2.9 Units
**ARPKZ** 35359

**Autosomal Recessive Polycystic Kidney Disease (ARPKD), Full Gene Analysis**

**Clinical Information:** Autosomal recessive polycystic kidney disease (ARPKD) is a disorder caused by mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene. The incidence of ARPKD is approximately 1:20,000 and the estimated carrier frequency in the general population is 1:70. ARPKD is characterized by enlarged echogenic kidneys, congenital hepatic fibrosis, and pulmonary hypoplasia (secondary to oligohydramnios [insufficient volume of amniotic fluid] in utero). Most individuals with ARPKD present during the neonatal period and, of those, nearly one-third die of respiratory insufficiency. Early diagnosis, in addition to initiation of renal replacement therapy (dialysis or transplantation) and respiratory support, increases the 10-year survival rate significantly. Presenting symptoms include bilateral palpable flank masses in infants and subsequent observation of typical findings on renal ultrasound, often within the clinical context of hypertension and prenatal oligohydramnios. In rarer cases, individuals may present during childhood or adulthood with hepatosplenomegaly. Of those who survive the neonatal period, one-third progress to end-stage renal disease and up to one-half develop chronic renal insufficiency. The PKHD1 gene maps to 6p12 and includes 67 exons. The PKHD1 gene encodes a protein called fibrocystin, which is localized to the primary cilia and basal body of renal tubular and biliary epithelial cells. Because ARPKD is an autosomal recessive disease, affected individuals must carry 2 deleterious mutations within the PKHD1 gene. Although disease penetrance is 100%, intrafamilial variation in disease severity has been observed. Mutation detection is often difficult due to the large gene size and the prevalence of private mutations that span the entire length of the gene.

**Useful For:** Diagnosis of individuals suspected of having autosomal recessive polycystic kidney disease (ARPKD) Prenatal diagnosis if there is a high suspicion of ARPKD based on ultrasound findings Carrier testing of individuals with a family history of ARPKD but an affected individual is not available for testing or disease-causing mutations have not been identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**FAVI** 91509

**Avian Panel (5 Bird Antigens), Serum**

**Reference Values:**

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 213
This panel includes the following antigens:
- Pigeon DE
- Parakeet
- Cockatiel
- Parrot
- Pigeon Sera

This result must be correlated with patient’s clinical response and should not solely be considered in the diagnosis.

**FAVCG**

**Avocado IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**AVOC**

**Avocado, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>
AXIN2 Gene, Full Gene Analysis

Clinical Information: Oligodontia, defined as the congenital absence of 6 or more permanent teeth, can occur as either an isolated finding or as part of an underlying syndrome. AXIN2 is one of several genes that have been associated with nonsyndromic oligodontia. In a subset of patients, mutations in the AXIN2 gene have been found to be associated with a combined oligodontia-colorectal cancer syndrome. Oligodontia-colorectal cancer syndrome is a rare hereditary cancer syndrome. One study of a Finnish family with AXIN2-related oligodontia-colorectal cancer syndrome identified colorectal cancer in 67% (6 of 9) of family members with oligodontia and a confirmed AXIN2 mutation. The AXIN2 mutation in this family was inherited in an autosomal dominant fashion. In the same study, a de novo AXIN2 mutation was identified in a 13-year-old patient with oligodontia but no history of colorectal cancer. Somatic AXIN2 mutations have been identified in mismatch repair-deficient colorectal tumors and have been shown to cause accumulation of beta-catenin and subsequent activation of T-cell factor-dependent transcription. These findings support the role of AXIN2 in tumorigenesis.

Useful For: Confirmation of oligodontia-colorectal cancer syndrome in patients with clinical features

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Azathioprine (Imuran) as 6-Mercaptopurine

Reference Values:
Units: ng/mL

Azathioprine is measured as the metabolite, 6-mercaptopurine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses produce 6-mercaptopurine serum concentrations of less than 1000 ng/ml.
Clinical Information: B-cell lymphoblastic leukemia/lymphoma (B-ALL) is a neoplasm of precursor cells (lymphoblasts) committed to B-cell lineage. B-ALL is the most common acute leukemia in children and adolescents, and also occurs in adults. Patients with B-ALL typically present with a high blast count in the peripheral blood, and bone marrow replacement with the disease. The diagnosis of B-ALL is based on a combination of morphologic features showing primarily small blasts with open chromatin and high N:C ratio, and an immunophenotype showing immaturity (CD34 and/or TdT expression) associated with B-cell lineage markers (CD19, CD22, and CD79a). New therapeutic approaches in B-ALL have been increasingly successful. One of the most important predictors of the disease relapse is the ability to detect minimal residual disease (MRD) in the bone marrow specimens following induction phase of the therapy (day 28). Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD (at 0.01% sensitivity) is an important prognostic indicator in these patients. This test is used to establish an antigen footprint of tumor cells at diagnosis to monitor minimal residual disease in these patients after treatments and/or transplants.

Useful For: Aiding in the monitoring of a previously confirmed diagnosis of B-cell lymphoblastic leukemia

Interpretation: An interpretive report for presence or absence of B lymphoblastic leukemia minimal residual disease (MRD) is provided. Patients who have detectable MRD by this assay are considered to have residual/recurrent B-ALL.

Reference Values: An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). It has a peak incidence at 2 to 5 years of age. The incidence decreases with increasing age, before increasing again at around 50 years of age. ALL is slightly more common in males than females. There is an increased incidence of ALL in individuals with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for ALL in children is about 90% and about 45% to 60% of adults have long-term disease-free survival. CRLF2/IGH rearrangements are more commonly observed in patients with Down syndrome or of Hispanic descent. Specific genetic abnormalities are identified in the majority of cases of B-ALL, either by conventional chromosome studies or FISH studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), MLL translocations, RUNX1 duplication/amplification or a hypodiploid clone is identified. In contrast, if ETV6/RUNX1 fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the B-ALL clone for the important prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Common Chromosome Abnormalities in B-cell Acute Lymphoblastic Leukemia Cytogenetic change Typical demographic Risk category t(12;21)(p13;q22), ETV6(TEL)/RUNX1(AML1) Pediatric Favorable Hyperdiploidy Pediatric Favorable (1;19)(q23;p13.3), PBX1/TCF3 Pediatric Intermediate t(9;22)(q34;q11.2) BCR/ABL1 Pediatric/Adult Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A(p16) All ages Variable t(11q23;var), MLL All ages Unfavorable t(9;11)(q21;q23), AFF1(AF4)/MLL All ages Unfavorable t(6;11)(q27;q23), MLLT4/MLL All ages Unfavorable t(9;11)(p22;q23), MLLT3(AF9)/MLL All ages Unfavorable t(10;11)(p12;q23), MLLT10/MLL All ages Unfavorable t(11;19)(q23;p13.1), MLL/EML All ages Unfavorable t(11;19)(q23;p13.3), MLL/MLLT1(ENL) All ages Unfavorable t(14q32;var), IGH All ages Variable (t;14)(p22;q32)(t(Y;14)(p11;q32), CRLF2/IGH Adolescent/Young Adult Unfavorable del(17p), TP53 All ages Unfavorable Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with B-cell acute lymphoblastic leukemia (B-ALL) Identifying and tracking known chromosome abnormalities in patients with B-ALL and tracking response to therapy As an adjunct to conventional chromosome studies in patients with B-ALL

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values: An interpretive report will be provided.

B-Cell CD40 Expression by Flow Cytometry, Blood

Clinical Information: The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer [NK] cells) and humoral (mediated by B cells) immunity. After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells. Decreased numbers or aberrant function of B cells result in humoral immune deficiency states with increased susceptibility to infections, and these may be either primary (genetic) or secondary immunodeficiencies. Secondary causes include medications, malignancies, infections, and autoimmune disorders (this does not cause immunodeficiency with increased infection). CD40 is a member of the tumor necrosis factor receptor superfamily, expressed on a wide range of cell types including B cells, macrophages, and dendritic cells.(1) CD40 is the receptor for CD40 ligand (CD40LG), a molecule predominantly expressed by activated CD4+ T cells. CD40/CD40LG interaction is involved in the formation of memory B lymphocytes and promotes immunoglobulin (Ig) isotype switching.(1) CD40LG expression in T cells requires cellular activation, while CD40 is constitutively expressed on the surface of B cells and other antigen-presenting cells. Hyperimmunoglobulin M (hyper-IgM or HIGM) syndrome is a rare primary immunodeficiency characterized by increased or normal levels of IgM with low IgG and/or IgA.(2) Patients with hyper-IgM syndromes may have genetic defects or mutations in 1 of several known genes. Some of these genes are CD40LG, CD40, AICDA (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and IKBKG (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma; also known as NEMO).(2) Not all cases of hyper-IgM syndrome fit into these known genetic defects. Mutations in CD40LG and IKBKG are inherited in an X-linked fashion, while mutations in the other 3 genes are autosomal recessive. Elevated IgM is only one of the features of NEMO deficiency and therefore, it is no longer classified exclusively with the hyper-IgM syndromes. Distinguishing between the different forms of hyper-IgM syndrome is very important because of differing prognoses. CD40 and CD40LG deficiency are among the more severe forms, which typically manifest in infancy or early childhood, and are characterized by an increased susceptibility to opportunistic pathogens (eg, Pneumocystis carinii, Cryptosporidium, and Toxoplasma gondii).(3) CD40 deficiency, also known as hyper-IgM type 3 (HIGM3), accounts for <1% of hyper-IgM syndromes. Flow cytometry analysis shows complete lack of CD40 expression on the B cells of these patients.(4) Intravenous injection with IgG is the treatment of choice along with immune reconstitution with hematopoietic cell transplantation. To date, all documented CD40-deficient patients have been diagnosed before age 1. Consequently, when used in the context of HIGM3, this test is only indicated in children (for diagnosis). In the case of CD40L deficiency, this test can be used for male patients or in females of child-bearing age (to identify carriers). A larger age spectrum has been reported with CD40L deficiency, ranging from infancy to early adulthood. CD40 expression on B cells is also an indicator of immune status (eg, after the use of biological immunomodulatory therapy for autoimmune disease, cancer and transplantation).

Useful For: Evaluating patients for hyper-IgM type 3 (HIGM3) syndrome due to defects in CD40, typically seen in patients <10 years of age Assessing B-cell immune competence in other clinical contexts, including autoimmunity, malignancy and transplantation

Interpretation: This assay is qualitative; CD40 expression is reported as present (normal) or absent (abnormal). Normal B cells express surface CD40 on the majority of cells. Hyper-IgM (HIGM3) syndrome patients typically do not express CD40 on the surface of B cells. Genotyping of CD40 is required for a definite diagnosis of HIGM3. Contact Mayo Medical Laboratories for ordering assistance.

Reference Values:
Present (normal)

B-Cell Lymphoma, FISH, Blood or Bone Marrow

Clinical Information: Lymphoid neoplasms are known to be complex and the prognosis and clinical course of patients with lymphoma is highly variable. Genetic abnormalities have emerged as one of the most reliable criteria for categorizing lymphomas. Several chromosome abnormalities and variants of these abnormalities have been associated with various kinds of lymphoma (see Table). Common Chromosome Abnormalities in B-cell Lymphomas

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Chromosome Abnormality</th>
<th>FISH Probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt (pediatric, ≤18 years old)</td>
<td>8q24.1 rearrangement 5αTIM/3αTIM MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3αTIM/5αTIM BCL6 18q21 rearrangement 3αTIM/5αTIM BCL2 Diffuse large B-cell, Burkitt-like &quot;double-hit&quot;</td>
<td>8q24.1 rearrangement 5αTIM/3αTIM MYC Reflex: t(2;8)(p12;q24.1) IGK/MYC Reflex: t(8;14)(q24.1;q32) MYC/IGH Reflex: t(8;22)(q24.1;q11.2) MYC/IGL Reflex: 3q27 rearrangement 3αTIM/5αTIM BCL6 Reflex: 18q21 rearrangement 3αTIM/5αTIM BCL2 3q27 rearrangement 3αTIM/5αTIM BCL6 Mantle Cell t(11;14)(q13;q32) CCND1/IGH Reflex: 11q13 rearrangement 5αTIM/3αTIM CCND1 Blastosid subtype only: deletion of 17p TP53/D17Z1 Blastosid subtype only: 8q24.1 rearrangement 5αTIM/3αTIM MYC MALT 18q21 rearrangement 5αTIM/5αTIM MALT1 Splenic Marginal Zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1</td>
</tr>
<tr>
<td>Diffuse large B-cell, Burkitt-like &quot;double-hit&quot;</td>
<td>8q24.1 rearrangement 5αTIM/3αTIM MYC Reflex: t(2;8)(p12;q24.1) IGK/MYC Reflex: t(8;14)(q24.1;q32) MYC/IGH Reflex: 3q27 rearrangement 3αTIM/5αTIM BCL6 18q21 rearrangement 3αTIM/5αTIM BCL2 Diffuse large B-cell, Burkitt-like &quot;double-hit&quot;</td>
<td>8q24.1 rearrangement 5αTIM/3αTIM MYC MALT 18q21 rearrangement 5αTIM/5αTIM MALT1 Splenic Marginal Zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1</td>
</tr>
</tbody>
</table>

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various B-cell lymphomas Tracking known chromosome abnormalities and response to therapy in patients with B-cell neoplasms

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone supports a diagnosis of a B-cell neoplasm; the specific abnormality detected may help subtype the neoplasm The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.


B-Cell Lymphoma, FISH, Tissue

Clinical Information: Mature B-cell lymphoma can be low grade, intermediate grade, or high grade, and the prognosis and clinical course are highly variable. Genetic abnormalities have emerged as one of the most important prognostic markers in B-cell lymphomas and can aid in diagnosis. Several chromosome abnormalities and variants of these abnormalities have been associated with various lymphoma subtypes (see table). Conventional chromosome studies cannot be employed on paraffin-embedded tissue, and molecular genetic analyses are often problematic in the study of lymphomas. FISH permits the detection of abnormal gene associated with various chromosome translocations and inversions in B-cell lymphoma (see table). Common Chromosome Abnormalities in B-cell Lymphomas Type Chromosome Abnormality FISH Probe Burkitt (pediatric, ≤18 years old) 8q24.1 rearrangement 5αTIM/3αTIM MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3αTIM/5αTIM BCL6 18q21 rearrangement 3αTIM/5αTIM BCL2 Diffuse large B-cell, Burkitt-like "double-hit" 8q24.1 rearrangement 5αTIM/3αTIM MYC Reflex: t(2;8)(p12;q24.1) IGK/MYC Reflex: t(8;14)(q24.1;q32) MYC/IGH Reflex: 3q27 rearrangement 3αTIM/5αTIM BCL6 Reflex: 18q21 rearrangement 3αTIM/5αTIM BCL2 3q27 rearrangement 3αTIM/5αTIM BCL6 Mantle Cell t(11;14)(q13;q32) CCND1/IGH Reflex: 11q13 rearrangement 5αTIM/3αTIM CCND1 Blastosid subtype only: deletion of 17p TP53/D17Z1 Blastosid subtype only: 8q24.1 rearrangement 5αTIM/3αTIM MYC MALT 18q21 rearrangement 5αTIM/5αTIM MALT1 Splenic Marginal Zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1
t(8;22)(q24.1;q11.2) MYC/IGL Reflex: 3q27 rearrangement 3αε™/5αε™ BCL6 Reflex: 18q21 rearrangement 3αε™/5αε™ BCL2 Follicular 18q21 rearrangement 3αε™/5αε™ BCL2 3q27 rearrangement 3αε™/5αε™ BCL6 Mantle Cell t(11;14)(q13;q32) CCND1/IGH Blastoid subtype only: deletion of 17p TP53/D17Z1 Blastoid subtype only: 8q24.1 rearrangement 5αε™/3αε™ MYC MALT 18q21 rearrangement 5αε™/3αε™ MALT1 Splenic Marginal Zone Deletion of 7p D7Z1/7q32 Deletion of 17p TP53/D17Z1

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various B-cell lymphomas Tracking known chromosome abnormalities and response to therapy in patients with B-cell lymphomas

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone is supportive of a diagnosis of a B-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years of age, or occasionally even later. Four different genetic defects have been associated with CVID including mutations in the ICOS, CD19, BAFF-R, and TACI genes. The first 3 genetic defects account for approximately 1% to 2%, and TACI mutations account for 8% to 15% of CVID cases. CVID is characterized by hypogammaglobulinemia usually involving most or all of the Ig classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1,2) B-cell numbers may be normal or decreased. A minority of CVID patients (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency.(1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4 to CD8 ratio (<1). Studies have shown the clinical relevance of classifying CVID patients by assessing B-cell subsets, since changes in different B-cell subsets are associated with particular clinical phenotypes or presentations.(3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA.(5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects--mutations in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes.(5) Mutations in CD40L and NEMO are inherited in an X-linked fashion, while mutations in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increased in nonswitched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depleting therapies, such as Rituxan (Rituximab) and Zevalin (Ibritumomab tiuxetan). CVID Confirmation Flow Panel: The etiology of CVID is heterogeneous, but recently 4 genetic defects were described that are associated with the CVID phenotype. Specific mutations, all of which are expressed on B cells, have been implicated in the pathogenesis of CVID. These mutations encode for: -ICOS-inducible costimulator expressed on activated T cells(1) -TACI-transmembrane activator and CAML (calcium modulator and cyclophilin ligand) interactor(2) -CD19(3) -BAFF-R-B cell activating factor belonging to the tumor necrosis factor (TNF) receptor family(4) Of these, the TACI mutations probably account for about 10% of all CVID cases.(2) Patients with mutations in the TACI gene are particularly prone to developing autoimmune disease, including cytopenias as well as lymphoproliferative disease. The other mutations each have been reported in only a handful of patients. The etiopathogenesis is still undefined in more than 50% of CVID patients. A BAFF-R defect should be suspected in patients with low to very low class switched and nonswitched memory B cells and very high numbers of transitional B cells (see IABC/87994 B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood). Class switching is the process that allows B cells, which possess IgD and IgM on their cell surface as a part of the antigen-binding complex, to produce IgA, IgE, or IgG antibodies. A TACI defect is suspected in patients with low IgM with normal to low switched B cells, with autoimmune and/or lymphoproliferative manifestations, and normal B cell responses to mitogens. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(5) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(6-8) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(6) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(9) and during summer compared to winter.(10) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Screening for common variable immunodeficiency (CVID) and hyper-IgM syndromes Assessing B-cell subset reconstitution after stem cell or bone marrow transplant Assessing response to B-cell-depleting immunotherapy Identifying defects in transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI) and B-cell-activating factor receptor (BAFF-R) in patients presenting with clinical symptoms and other laboratory features consistent with CVID.
**Interpretation:** T- and B-Cell Quantitation by Flow Cytometry: When the CD4 count falls below 500 cells/mcL, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended. Immune Assessment B Cell Subsets, Blood: The assay provides quantitative information on the various B-cell subsets (percentage and absolute counts in cells/microliter). Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: CD19+=B cells expressing CD19 as a percent of total lymphocytes -CD19+ CD27+=total memory B cells -CD19+ CD27+ IgD+ IgM+=marginal zone or nonswitched memory B cells -CD19+ CD27+ IgD-IgM+=IgM-only memory B cells -CD19+ CD27+ IgD-IgM+=class-switched memory B cells -CD19+ IgM+=IgM B cells -CD19+ CD38+ IgM+=transitional B cells -CD19+ CD38+ IgM+=plasmablasts -CD19+ CD21+=CD21 low (“immature”) B cells -CD19+ CD21+=mature B cells -CD19+ CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes For isotype class-switching and memory B-cell analyses, the data will be reported as being consistent or not consistent with a defect in memory and/or class switching. If a defect is present in any of these B-cell subpopulations, further correlation with clinical presentation and additional functional, immunological, and genetic laboratory studies will be suggested. Since each of the 11 B-cell subsets listed above contributes to the diagnosis of common variable immunodeficiency (CVID) and hyper-IgM syndromes and provides further information on the likely specific genetic defect, all the B-cell subsets are carefully evaluated to determine if further testing is needed for confirmation, including functional assays and genotyping, which is then suggested as follow-up testing in the interpretive report as detailed below. If abnormalities are found in the B-cell phenotyping panel, the specimen will be reflexed to the CVID confirmation panel for assessment of defects in surface expression of B-cell-activating factor receptor (BAFF-R) and transmembrane activator and calcium modulator and cyclophilin ligand (CAMLI) interactor (TACI) (2 genes/proteins associated with CVID). To conclusively determine if TACI mutations are present, the TACI mutation analysis test by gene sequencing can be ordered (TACI / Transmembrane Activator and CAMLI Interactor [TACI] Gene, Full Gene Analysis). CVID Confirmation Flow Panel: BAFF-R is normally expressed on over 95% of B cells, while TACI is expressed on a smaller subset of B cells and a proportion of activated T cells. The lack of TACI or BAFF-R surface expression on the appropriate B-cell population is consistent with a CVID defect. Results will be interpreted in the context of the B-cell phenotyping results and correlation to clinical presentation will be recommended.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.


**BNP 83873**

**B-Type Natriuretic Peptide (BNP), Plasma**

**Clinical Information:** B-type natriuretic peptide (brain natriuretic peptide; BNP) is a 32-amino acid-ringed peptide secreted by the heart to regulate blood pressure and fluid balance.(1) BNP is stored in and secreted predominantly from membrane granules in the heart ventricles, and is continuously released from the heart in response to both ventricle volume expansion and pressure overload.(2) The natriuretic peptide system and the renin-angiotensin system counteract each other in arterial pressure regulation. When arterial pressure decreases, the kidneys release renin, which activates angiotensinogen resulting in increased peripheral resistance of the arterioles, thus increasing arterial pressure. The natriuretic peptides counteract the effects of renin secretion, causing a reduction of blood pressure and in extracellular fluid volume.(3) Both BNP and atrial natriuretic peptide (ANP) are activated by atrial and ventricular distension due to increased intracardiac pressure. These peptides have both natriuretic and diuretic properties: they raise sodium and water excretion by increasing the glomerular filtration rate and inhibiting sodium reabsorption by the kidney. The New York Heart Association (NYHA) developed a functional classification system for congestive heart failure (CHF) consisting of 4 stages based on the severity of the symptoms. Various studies have demonstrated that circulating BNP concentrations increase with the severity of CHF based on the NYHA classification.(4-6)

**Useful For:** Aids in the diagnosis of congestive heart failure (CHF) The role of brain natriuretic peptide in monitoring CHF therapy is under investigation

**Interpretation:** >normal <200 pg/mL: likely compensated congestive heart failure (CHF) > or =200 to < or =400 pg/mL: likely moderate CHF >400 pg/mL: likely moderate-to-severe CHF Brain natriuretic peptide (BNP) levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Interpretive Levels for CHF Functional Class 5th to 95th Percentile Median I 15 to 499
Elevation in BNP can occur due to right heart failure with cor pulmonale (200-500 pg/mL), pulmonary hypertension (300-500 pg/mL), and acute pulmonary embolism (150-500 pg/mL). Elevations also occur in patients with acute coronary syndromes.

**Reference Values:**

**Males**

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75 years: < or =137 pg/mL
76 years: < or =140 pg/mL
77 years: < or =144 pg/mL
78 years: < or =147 pg/mL
79 years: < or =151 pg/mL
80 years: < or =155 pg/mL
81 years: < or =159 pg/mL
82 years: < or =163 pg/mL
> or =83 years: < or =167 pg/mL


FBAB 91608

Babesia microti Antibodies (IgG, IgM)

Reference Values:
Reference Ranges
IgG: <1:64
IgM: <1:20

Elevated antibody levels to B. microti indicate exposure to the organism. Human babesiosis infection is transmitted by the bite of an infected Ixodes tick or less frequently from transfusion with blood from an infected donor. Definitive diagnosis is made by identifying intraerythrocytic organisms in peripheral blood. In patients with low parasitemia, antibody detection by IFA is recommended. IgG levels greater than or equal to 1:1024 can be detected in acute phase patients with parasites in blood smears. The IFA assay can be used as a seroepidemiologic tool to study the frequency and distribution of B. microti in endemic areas especially in persons with mixed infections also involving Borreliaburgdorferi.

BABG 81128

Babesia microti IgG Antibodies, Serum

Clinical Information: Babesiosis is a zoonotic infection caused by the protozoan parasite Babesia microti. The infection is acquired by contact with Ixodes ticks carrying the parasite. The deer mouse is the
animal reservoir and, overall, the epidemiology of this infection is much like that of Lyme disease. Babesiosis is most prevalent in the Northeast, Upper Midwest, and Pacific Coast of the United States. Infectious forms (sporozoites) are injected during tick bites and the organism enters the vascular system where it infects RBCs. In this intraerythrocytic stage it becomes disseminated throughout the reticuloendothelial system. Asexual reproduction occurs in RBCs, and daughter cells (merozoites) are formed which are liberated on rupture (hemolysis) of the RBC. Most cases of babesiosis are probably subclinical or mild, but the infection can be severe and life threatening, especially in older or asplenic patients. Fever, fatigue, malaise, headache, and other flu-like symptoms occur most commonly. In the most severe cases, hemolysis, acute respiratory distress syndrome, and shock may develop. Patients may have hepatomegaly and splenomegaly.

**Useful For:** A serologic test can be used as an adjunct in the diagnosis of babesiosis or in seroepidemiologic surveys of the prevalence of the infection in certain populations. Babesiosis is usually diagnosed by observing the organisms in infected RBCs on Giemsa-stained thin blood films of smeared peripheral blood. Serology may be useful if the parasitemia is too low to detect or if the infection has cleared naturally or following treatment. Serology may also be useful in the follow-up of documented cases of babesiosis or if chronic or persistent infection is suspected.

**Interpretation:** A positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2,560.

**Reference Values:**

<1:64


**LBAB 62847 Babesia species, Molecular Detection, PCR, Blood**

**Clinical Information:** Babesiosis is an emergent zoonosis caused by an intraerythrocytic protozoan in the genus Babesia. Babesia microti is responsible for the vast majority of human cases in the United States, with "hot spots" of disease along the Northeast Coast (eg, Martha's Vineyard, Long Island, and Nantucket) and the upper Midwestern states, although the distribution of disease is spreading. In addition, a small number of cases of Babesia duncani and Babesia duncani-like human infection (WA and CA strains) have been reported along Pacific Coast states from Washington to northern California, and Babesia divergens/Babesia divergens-like strains have been isolated from humans in Missouri (MO-1 strain), Kentucky, and Washington. At this time, only Babesia microti is a nationally notifiable disease. Babesia microti shares a tick vector with Borrelia burgdorferi and Anaplasma phagocytophilum, the causative agents of Lyme disease and human granulocytic anaplasmosis (HGA), respectively. Recent studies suggest that exposure to Babesia microti is quite common in areas endemic for Lyme disease and anaplasmosis, so it is prudent to consider testing for all 3 diseases concurrently. Less commonly, babesiosis may be acquired through blood transfusion, and therefore donor units are tested for this parasite in some endemic areas. Most patients with babesiosis have a mild illness or are asymptomatic, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. The definitive laboratory diagnosis of babesiosis rests on the demonstration of Babesia species characteristic intraerythrocytic parasites in Giemsa-stained thick and thin blood films. This method is capable of detecting (but not differentiating) human-infective Babesia species. Babesia may closely resemble those of Plasmodium falciparum. The Mayo Clinic real-time PCR assay provides a rapid and sensitive alternative to blood film examination and enables the detection and differentiation of Babesia microti, Babesia duncani/Babesia duncani-like and Babesia divergens/Babesia divergens-like parasites. It does not cross-react with malaria parasites. Finally, antibody testing may be used and is useful for detection of babesiosis, but may be negative in the early phase of illness and cannot distinguish active from past infection.
**Useful For:** An initial screening or confirmatory testing method for suspected babesiosis during the acute febrile stage of infection in patients from endemic areas, especially when Giemsa-stained peripheral blood smears do not reveal any organisms or the organism morphology is inconclusive.

**Interpretation:** A positive result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results and clinical findings. A negative result indicates absence of detectable DNA from Babesia species in the specimen, but does not always rule out ongoing babesiosis in a seropositive person, since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in the evaluation of a patient presenting with an acute febrile illness following tick exposure include serologic tests for Lyme disease (Borrelia burgdorferi), and molecular detection (PCR) for ehrlichiosis/anaplasmosis. For patients who are past the acute stage of infection, serologic tests for these organisms should be ordered prior to PCR testing.

**Reference Values:**

- Negative

**Clinical References:**

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**Bacterial Culture, Aerobic**

**Clinical Information:** Sterile Body Fluids and Normally Sterile Tissues: In response to infection, fluid may accumulate in any body cavity. Wound, Abscess, Exudates: Skin and soft tissue infections can occur as a result of a break in the skin surface, or they can occur as complications of surgery, trauma, human, animal, or insect bites, or diseases that interrupt a mucosal or skin surface. Specimen collection is of utmost importance for these specimen types. For most open lesions and abscesses, remove the superficial flora by decontaminating the skin before collecting a specimen from the advancing margin or base. A closed abscess is the specimen site of choice. Aspirate the abscess contents with a syringe.

**Useful For:** Detecting bacteria responsible for infections of sterile body fluids, tissues, or wounds

**Interpretation:** Any microorganism found where no resident flora is present is considered significant and is reported. For specimens contaminated with the usual bacterial flora, bacteria that are potentially pathogenic are identified.

**Reference Values:**

- No growth or usual flora
- Identification of probable pathogens

**Clinical References:** Forbes BA, Sahm DF, Weissfeld AS: Bailey and Scott's Diagnostic Microbiology. 12th edition. Mosby, St. Louis, MO, 2007, Chapters 55, 56, 58, 60,61

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**Bacterial Culture, Aerobic, Respiratory**

**Clinical Information:** Common bacterial agents of acute pneumonia include: Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, and members of the Enterobacteriaceae (Escherichia coli, Klebsiella species, and Enterobacter species) Clinical history,
physical examination, and chest X-ray are usually adequate for the diagnosis of pneumonia, and antimicrobial treatment is typically based on these findings. Culture of expectorated sputum is used by some for the evaluation of pneumonia, although controversy exists regarding this practice; both sensitivity and specificity of sputum cultures are generally regarded as poor (<50%). Specificity is improved by collecting expectorated purulent matter from the lower respiratory tract and avoiding mouth and oropharyngeal matter, thereby reducing contamination. Prior to culture, the specimen should be examined for the presence of WBCs (evidence of purulent matter) and a paucity of squamous cells (evidence of minimal contamination by oral matter). Blood cultures should be performed to establish the definitive etiology of an associated pneumonia. However, only 20% to 30% of patients with bacterial pneumonia are bacteremic.

**Useful For:** An aid in the diagnosis of lower respiratory bacterial infections including pneumonia

**Interpretation:** Organisms associated with lower respiratory tract infections are reported.

**Reference Values:**
- No growth or usual flora
- Identification of probable pathogens


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**Bacterial Culture, Aerobic, Urine**

**Clinical Information:** Urinary tract infection (UTI) encompasses a broad range of clinical entities that vary in their clinical presentation, degree of tissue invasion, epidemiologic setting, and antibiotic therapy requirements. There are 4 major types of UTIs: urethritis, cystitis, acute urethral syndrome, and pyelonephritis. UTIs may also be classified as uncomplicated or complicated. Escherichia coli is the leading cause of uncomplicated community-acquired UTI. Risk factors that predispose one to complicated UTIs include: underlying diseases that are associated with kidney infection (eg, diabetes), kidney stones, structural or functional urinary tract abnormalities, and indwelling urinary catheters. Another classification of UTIs is as upper UTI (related to the kidney, renal pelvis, or ureter) or lower UTI (urinary bladder and urethra). The classic symptoms of upper UTI are fever (often with chills) and flank pain; frequent painful urination, urgency, and dysuria are more often associated with lower UTI.

**Useful For:** Diagnosis of urinary tract infections Quantitative culture results may be helpful in discriminating contamination, colonization, and infection.

**Interpretation:** In general, the isolation of >100,000 cfu/mL of a urinary pathogen is indicative of urinary tract infection. Isolation of 2 or more organisms >10,000 cfu/mL may suggest specimen contamination.

**Reference Values:**
- No growth
- Identification of probable pathogens with colony count ranges


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**Bacterial Culture, Anaerobic**

**Clinical Information:** Anaerobic bacteria are the greatest component of the human body's normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are penetrated and in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include...
periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes and by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and they are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians. Many Bacteroides species produce beta-lactamases. Imipenem, metronidazole, and clindamycin are effective agents although resistance to clindamycin, and occasionally imipenem, is increasing.

Useful For: Diagnosing anaerobic bacterial infections

Interpretation: Isolation of anaerobes in significant numbers from well-collected specimens including blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with that (those) organisms.

Reference Values:
No growth
Identification of probable pathogens

Clinical References:

BBLD 8082 Bacterial Culture, Blood
Clinical Information: Bacteremia results when bacteria multiply at a rate that exceeds removal by phagocytes. The clinical pattern of bacteremia may be transient, intermittent, or continuous. Transient bacteremia often occurs after manipulative procedures (dental procedures, cystoscopy) or surgery in contaminated areas of the body. Undrained abscesses (intraabdominal, pelvic, hepatic) may result in intermittent bacteremia. A hallmark feature of subacute bacterial endocarditis is a continuous bacteremia. The sources of bacteremia are genitourinary tract (25%), respiratory tract (20%), abscesses (10%), surgical wounds (5%), biliary tract (5%), other known sites (10%), and unknown sites (25%).

Useful For: Diagnosis and treatment of the etiologic agent of sepsis

Interpretation: Microbial growth is reported.

Reference Values:
No growth
Identification of all organisms


CFRC 89653 Bacterial Culture, Cystic Fibrosis, Respiratory
Clinical Information: Life expectancy of patients with cystic fibrosis (CF) has increased steadily over the past 50 years, in large part due to improvements in the management of lung disease in this patient population. Still, chronic lung infection is responsible for 75% to 85% of deaths in patients with CF. Appropriate treatment for the causative organism can reduce morbidity and mortality. The number of microbial species associated with CF lung disease is relatively limited. These include Pseudomonas aeruginosa (mucoid and nonmucoid), Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia, other nonfermenting gram-negative rods, Haemophilus influenzae, and Streptococcus pneumoniae. Nontuberculous mycobacteria and Aspergillus species may also play a role in
CF lung disease, in addition to common respiratory viruses. This culture, which is specifically designed for CF patients, utilizes conventional and additional selective media (compared to non-CF respiratory cultures) to isolate bacteria commonly associated with pulmonary disease in CF patients. In selected centers, lung transplantation is performed on CF patients. This test is appropriate for lung transplant patients with underlying CF because they can continue to harbor the same types of organisms as they did pretransplantation. CF patients may be colonized or chronically infected by these organisms over a long period of time.

**Useful For:** Detection of aerobic bacterial pathogens from cystic fibrosis patient specimens

**Interpretation:** A negative test result is no growth of bacteria or growth of only usual flora. A negative result does not rule out all causes of infectious lung disease (see Cautions). Organisms associated with lower respiratory tract infections are reported. For positive test results, pathogenic bacteria are identified. Cystic fibrosis patients may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results.

**Reference Values:**
- No growth or usual flora
- Identification of probable pathogens

**Clinical References:**

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**Bacterial Typing by Pulsed-Field Gel Electrophoresis (PFGE)**

**Clinical Information:** Bacterial-typing techniques are useful for determining strain relatedness in the setting of nosocomial outbreaks or apparent outbreaks. Serial isolates obtained from the same patient can be typed to determine whether they are the same or different. Typing often allows the physician to discriminate between 2 species, recognize an outbreak, or identify the source of infection. In the past, strain typing was accomplished by testing for different biochemical, phage, or antibiotic resistance patterns. Antibiograms are often unreliable because they are easy to over-interpret or under-interpret. Other strain-typing methods are often organism-specific and each requires a unique set of reagents and procedures. The availability of classical strain-typing techniques has been limited. An excellent example of the power of the technique was in the analysis of a large number of clustered isolates of methicillin-resistant Staphylococcus aureus obtained from patients and staff at a Mayo Rochester hospital during September and October, 1992. Although the high frequency with which this organism was isolated suggested a nosocomial outbreak, molecular typing of the isolates showed: only 3 of the 14 were identical; the remaining isolates were most likely the result of a surge in the number of random isolates of this organism. Thus, the 14 isolates were not part of a nosocomial epidemic due to a single strain, and radical measures for control of a nosocomial outbreak were unnecessary.

**Useful For:** Bacterial typing is useful to investigate infection outbreaks by a single species.

**Interpretation:** Isolates which show identical DNA restriction fragment length polymorphism patterns are considered to be closely related.

**Reference Values:**
Reported as isolates from these sources are "indistinguishable" or "different" by pulsed-field gel electrophoresis. Results will be faxed to the client.

**Clinical References:**
2. Arbeit RD: Laboratory procedures for the

**Bahia Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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| 6     | > or =100| Strongly positive Reference values apply to all ages.


**Baker's Yeast, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**BCYP 82722**

**Bald Cypress, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
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Reference values apply to all ages.


**Bamboo Shoot, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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FBANG 57635 Banana IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values: <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

BANA 82746 Banana, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of July 8, 2016 11:28 am CDT
Barbiturates Confirmation, Chain of Custody, Urine

Clinical Information: Barbiturates represent a class of drugs that were originally introduced as sleep inducers. Butalbital is also used to control severe headaches. Meprobamate and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as "downers" to induce sleep after an amphetamine- or cocaine-induced "high." Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital Chain-of-custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of a barbiturate in urine at >200 ng/mL indicates use of 1 of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

Reference Values:
Negative
Cutoff concentrations:

**IMMUNOASSAY SCREEN**
<200 ng/mL

**BUTALBITAL BY GC-MS**
<100 ng/mL

**AMOBARBITAL BY GC-MS**
<100 ng/mL

**PENTOBARBITAL BY GC-MS**
<100 ng/mL

**SECOBARBITAL BY GC-MS**
<100 ng/mL

**PHENOBARBITAL BY GC-MS**
<100 ng/mL


Barbiturates Confirmation, Urine

Clinical Information: Barbiturates represent a class of drugs that were originally introduced as sleep inducers. Butalbital is also used to control severe headaches. Mephobarbital and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as "downers" to induce sleep after an amphetamine- or cocaine-induced "high."

Useful For: Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital

Interpretation: The presence of a barbiturate in urine at >200 ng/mL indicates use of 1 of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

Reference Values:

Negative

Cutoff concentrations:
BUTALBITAL BY GC-MS
<100 ng/mL

AMOBARBITAL BY GC-MS
<100 ng/mL

PENTOBARBITAL BY GC-MS
<100 ng/mL

SECOBARBITAL BY GC-MS
<100 ng/mL

PHENOBARBITAL BY GC-MS
<100 ng/mL


Barium, Serum

Reference Values:

Units: ng/mL

Reference range has not been established.

Barley Grass, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**FBARG 57578 Barley IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**BRLY 82687 Barley, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and...
bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**FBART 91439**

**Bartonella Antibody Panel, IFA CSF**

**Reference Values:**

REFERENCE RANGE: <1:1

**INTERPRETIVE CRITERIA:**

<1:1 Antibody Not Detected

> or = 1:1 Antibody Detected

Infection with Bartonella henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis and febrile bacteremia syndrome. Infection with Bartonella quintana has been associated with trench fever and bacillary angiomatosis in both HIV positive and negative individuals.

IgG crossreactivity between B. henselae and B. Quintana may occur at any titer; however, the infecting species will typically have the higher IgG titer. Crossreactivity of IgM between the two species is limited and typically is not seen.

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. However, interpreting results is complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps.
**Bartonella Antibody Panel, IgG and IgM, Serum**

**Clinical Information:** Bartonella henselae and Bartonella quintana are small, rod-shaped, pleomorphic, gram-negative bacteria. The human body louse (Pediculus humanis) is the proposed vector for Bartonella quintana. No animal reservoir has been determined for Bartonella quintana. The domestic cat is believed to be both a reservoir and vector for Bartonella henselae. Cats may infect humans directly through scratches, bites, or licks, or indirectly through an arthropod vector. Humans remain the only host in which Bartonella infection leads to significant disease. The sight of entry for Bartonella is through openings in the skin. Microscopically, Bartonella lesions appear as rounded aggregates that proliferate rapidly. These aggregates are masses of Bartonella bacteria. Warthin-Starry staining has shown that Bartonella organisms can be present within the vacuoles of endothelial cells, in macrophages, and between cells in areas of necrosis. Occasionally organisms are seen in the lumens of vessels. While cutaneous lesions are common, disseminated tissue infection by Bartonella has been seen in the blood, lymph nodes, spleen, liver, bone marrow, and heart. Bartonella henselae has been associated with cat scratch disease (CSD), peliosis hepatitis (PH), and endocarditis. Bartonella quintana has been associated with trench fever, bacillary angiomatosis (BA), and endocarditis. Both can cause BA, a newly recognized syndrome. BA is a vascular proliferative disease usually involving the skin and regional lymph nodes. CSD begins as a cutaneous papule or pustule that usually develops within a week after an animal contact. Regional lymphadenopathy, which follows, is the predominant clinical feature of CSD. Skin testing has been used in the past for CSD, but no skin test has been licensed for routine use. Trench fever, which was a problem during World War I and World War II, is characterized by a relapsing fever and severe pain in the shins. Interest in Bartonella quintana and Bartonella henselae has recently increased since its presence in AIDS patients and transplant patients has been documented. PH and febrile bacteremia syndrome are both syndromes that have afflicted patients with AIDS or those patients that are immunocompromised. While trench fever and CSD are usually self-limiting illnesses, the other Bartonella-associated diseases can be life-threatening.

**Useful For:** Rapid diagnosis of Bartonella infection, especially in the context of a cat scratch or histopathology showing typical features of stellate microabscesses and/or positive Warthin-Starry stain

**Interpretation:** A positive immunofluorescence assay (IFA) IgM (titer > 1:20) suggests a current infection with either Bartonella henselae or Bartonella quintana. A positive IgG (titer > 1:128) suggests a current or previous infection. Increases in IgG titers in serial specimens would indicate an active infection. Normal serum specimens usually have an IgG titer of < 1:128. However, 5% to 10% of healthy controls exhibit a Bartonella henselae and Bartonella quintana titer of 1:128. No healthy controls showed titers of > or =1:256. IgM titers from normal serum were found to be < 1:20. IgM titers at > or =1:20 have not been seen in the normal population. Culture should also be considered, but this may not be an optimal method due to slow growth and fastidious nature of the organism.

**Reference Values:**

<table>
<thead>
<tr>
<th>Bartonella henselae</th>
<th>Bartonella quintana</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG: &lt; 1:128</td>
<td>IgG: &lt; 1:128</td>
</tr>
<tr>
<td>IgM: &lt; 1:20</td>
<td>IgM: &lt; 1:20</td>
</tr>
</tbody>
</table>

endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue or serology. However, these methods may be falsely negative or nonspecific, respectively. Culture is insensitive. Evaluation of infected tissue using PCR has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Medical Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase gene present in Bartonella species.

**Useful For:** Diagnosing Bartonella infection

**Interpretation:** A positive test indicates the presence of Bartonella species DNA. A negative test indicates the absence of detectable DNA, but does not negate the presence of the organism or recent disease as false-negative results may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**BARTB**

**Bartonella, Molecular Detection, PCR, Blood**

**Clinical Information:** Bartonella henselae and Bartonella quintana are small, pleomorphic, gram-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. Bartonella henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. Bartonella quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue and serology. However, these methods may be nonspecific or falsely negative, especially in the early stages of disease. Evaluation of infected tissue or blood using PCR has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Medical Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase (gltA) gene present in Bartonella species.

**Useful For:** Diagnosing Bartonella infection where Bartonella DNA would be expected to be present in blood, especially endocarditis

**Interpretation:** A positive test indicates the presence of Bartonella species DNA. A negative test indicates the absence of detectable DNA, but does not negate the presence of the organism or recent disease as false-negative results may occur due to inhibition of PCR, sequence variability underlying primers and probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**
**Basil IgG**

**Interpretation:** mcg/mL of IgG

Lower Limit of Quantitation: 2.0

Upper Limit of Quantitation: 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Basil, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Bass Black (Sea Bass) (Centropristis striata) IgE**

**Interpretation:** Class IgE (kU/L) Comment
- 0 <0.35 Below Detection
- 1 0.35 - 0.69 Low Positive
- 2 0.70 - 3.49 Moderate Positive
- 3 3.50 - 17.49 Positive
- 4 17.50 - 49.99 Strong Positive
- 5 50.00 - 99.99 Very Strong Positive
- 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Bay Leaf, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**FBWME**  
Bayberry/Wax Myrtle (Myrica spp) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 17.5 - 49.9 50.0 - 99.9 > or = 100 Very High Positive Very High Positive Very High Positive Very High Positive

**Reference Values:**  
<0.35 kU/L

**BCRAB**  
BCR-ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myelogenous Leukemia (CML)

**Clinical Information:** Chronic myelogenous leukemia (CML) is a hematopoietic stem cell neoplasm included in the broader diagnostic category of myeloproliferative neoplasms. CML is consistently associated with fusion of the breakpoint cluster region gene (BCR) at chromosome 22q11 to the Abelson gene (ABL1) at chromosome 9q23. This fusion is designated BCR/ABL1 and may be seen on routine karyotype as the Philadelphia chromosome. Although various breakpoints within the BCR and ABL1 genes have been described, >95% of CMLs contain a consistent mRNA transcript in which either the BCR exon 13 (e13) or BCR exon 14 (e14) is fused to the ABL1 exon 2 (a2), yielding fusion forms e13/a2 and e14/a2, respectively. The e13/a2 and e14/a2 fusion forms produce a 210-kDa protein (p210). The p210 fusion protein is an abnormal tyrosine kinase known to be critical for the clinical and pathologic features of CML, and agents that block the tyrosine kinase activity (ie, tyrosine kinase inhibitors or TKI, such as imatinib mesylate), have been used successfully for treatment. Monitoring the level of BCR/ABL1 mRNA in CML patients during treatment is helpful for both prognosis and management of therapy.(1-3) Rising BCR-ABL1 mRNA levels following attainment of critical therapeutic milestones (see Clinical References) can be indicative of acquired resistance mutations involving the ABL1 part of the BCR-ABL1 fusion gene. Quantitative reverse-transcription PCR (qRT-PCR) is the most sensitive method for monitoring BCR-ABL1 mRNA levels during treatment. This test detects the BCR-ABL1 mRNA fusion forms found in CML (e13/a2 and e14/a2).

**Useful For:** Monitoring response to therapy in patients with chronic myeloid leukemia who are known to have the e13/a2 or e14/a2 BCR-ABL1 fusion transcript forms

**Interpretation:** An interpretive report will be provided. When BCR-ABL1 mRNA is present, quantitative results are reported on the international scale (IS), established from data originally reported in the IRIS (International Randomized Study of Interferon versus STI571) trial involving newly diagnosed chronic myeloid leukemia patients. Using the IS, a result <0.1% BCR-ABL1 (p210): ABL1 is equivalent to a major molecular remission. For further discussion of the international scale, see Clinical References.

**Reference Values:**  
The presence or absence of BCR-ABL1 mRNA fusion form e13/e14-a2 producing the p210 fusion protein is identified. If positive, the quantitative level is reported as the normalized ratio of BCR-ABL1 (p210) to endogenous ABL1 mRNA with conversion to a percentage referenced to the international scale (IS), on which 0.1% BCR-ABL1:ABL1 is designated as a major molecular response (MMR) threshold.

**Clinical References:**  
(RT-PCR), Quantitative, Monitoring Assay

Clinical Information: mRNA transcribed from BCR/ABL (fusion of the breakpoint cluster region gene [BCR] at chromosome 22q11 to the Abelson gene [ABL] at chromosome 9q23) is detected in all chronic myelogenous leukemia (CML) patients and a subset of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) patients. Although breakpoints in the BCR and ABL genes may occur in a variety of locations, splicing of the primary RNA transcripts result in only 8 fusion site variants (e1/a2, e6/a2, e13/a2, e14/a2, e19/a2, and e1/a3, e13/a3, e14/a3), which incorporate the entire sequence of the exons on both sides of the fusion site. The e1/a2 and e1/a3 fusion forms produce a 190-kDa protein designated p190. This bcr/abl protein form is found in approximately 75% of childhood ALL patients and approximately 50% of adult ALL patients, with the majority arising from e1/a2 mRNA. The p190 is also the predominant fusion form in a small subset of CML patients, although the vast majority of CML cases contain the p210 protein, typically from e13/a2 or e14/a2 mRNA fusions. Other fusion forms are very rare. Quantitative reverse-transcription PCR (qRT-PCR) is the most sensitive method for monitoring bcr/abl levels during treatment. This test detects mRNA coding for the most common p190 fusion form (e1/a2).

Useful For: Monitoring response to therapy in patients with known e1/a2 bcr/abl (p190) fusion forms

Interpretation: An interpretive report will be provided.

Reference Values: The presence or absence of the BCR/ABL mRNA (bcr/abl) fusion form producing the p190 fusion protein is reported. If positive, the level is reported as the ratio of bcr/abl (p190) to abl with conversion to a percentage (ie, bcr/abl (p190) as a percentage of total abl).


BCR/ABL1 Translocation (9;22), FISH

Clinical Information: Fusion of BCR/ABL1 is observed in all patients with chronic myeloid leukemia (CML), in approximately 25% of adult patients with precursor B-cell acute lymphoblastic leukemia (B-ALL) and in 1% of patients with pediatric B-ALL. The chromosome mechanism resulting in BCR/ABL1 fusion is a t(9;22)(q34;q11.2) in approximately 85%, a complex 9;22 translocation with 1 or more additional chromosomes in approximately 15% and a chromosomeally &eacute;crypticâ€• or insertional translocation in <1% of patients. Conventional cytogenetic studies are still the gold standard for identification of the t(9;22) and to monitor the effectiveness of treatment in post-therapy bone marrow specimens. FISH testing for BCR/ABL1 fusion or RT-PCR testing for p190 or p210 fusion forms are the recommended tests for evaluation of minimal residual disease following the disappearance of the t(9;22) in a post-treatment chromosome analysis. BCR/ABL1/ASS can be performed on bone marrow or peripheral blood and can be used to establish the percentage of neoplastic interphase nuclei for patients with CML at diagnosis and at all times during treatment, even in cytogenetic remission. BCR/ABL1/ASS can detect all known forms of the Ph chromosome, all atypical patterns associated with t(9;22)(q34q11.2) and can detect low levels of residual disease. We recommend BCR/ABL1/ASS at diagnosis subsequently to monitor the response to therapy.

Useful For: Detecting a neoplastic clone associated with a BCR/ABL1 rearrangement in patients with chronic myeloid leukemia (CML) Tracking the percentage of nuclei with BCR/ABL1 rearrangement and response to therapy in patients with CML It is recommended that conventional chromosome analysis CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow also be performed at initial diagnosis. FISH alone can be used to monitor the effectivness of therapy.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds...
the normal reference range. Additional cells are analyzed to assess minimal residual disease (MRD). The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BCR/ABL1, Qualitative, Diagnostic Assay**

**Clinical Information:** The t(9;22)/BCR-ABL1 abnormality is associated with chronic myelogenous leukemia (CML) and Philadelphia-positive acute lymphoblastic leukemia of B-cell lineage (Ph ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription PCR (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR-ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph ALL can have alternative break-fusion events resulting in unusual BCR-ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR-ABL1 mRNA transcripts, this assay also can identify these rarer BCR-ABL1 transcript variants and is therefore a comprehensive screen for both usual and uncommon BCR-ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors however, this assay will not identify extremely rare and unexpected BCR-ABL1 events involving other exons (eg, case report level) and is therefore not absolutely specific, but is predicted to detect >99.5% of BCR-ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR-ABL1 FISH or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR-ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which complementary methods cannot. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB, BA190). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality, or low cell number but it is not intended for quantitative or monitoring purposes.

**Useful For:** Diagnostic workup of patients with high probability of BCR-ABL1-positive hematopoietic neoplasms, predominantly chronic myelogenous leukemia and acute lymphoblastic leukemia. When positive, the test identifies which specific mRNA fusion variant is present to guide selection of an appropriate monitoring assay. If a quantitative monitoring assay is not available for a rare fusion variant, this assay may be of some value for monitoring.

**Interpretation:** An interpretive report will be provided.
**Reference Values:**
A qualitative result is provided that indicates the presence or absence of BCR/ABL mRNA. When positive, the fusion variant is also reported.

**Clinical References:**

**Clinical Information:**
Chronic myelogenous leukemia (CML) is characterized by the presence of the t(9:22) BCR-ABL1 abnormality, resulting in formation of a fusion BCR-ABL1 mRNA and protein. The ABL1 component of this oncoprotein contains tyrosine kinase activity and is thought to play a central role in the proliferative phenotype of this leukemia. Recent advances have resulted in a number of therapeutic drugs that inhibit the ABL1 tyrosine kinase, as well as other protein tyrosine kinases. Imatinib mesylate (Gleevec, Novartis) is the prototype of these tyrosine kinase inhibitors (TKIs), which are capable of inducing durable hematologic and (in most patients) cytogenetic remissions. Unfortunately, a significant subset of patients can develop functional resistance to TKIs, due in a large number of cases (approximately 50%) to the acquisition of point mutations in the kinase domain (KD) of the chimeric ABL1 gene. To date, over 50 distinct mutations have been described, although a smaller subset of these (<20) account for the majority of patients with clinical resistance to TKIs, or have well documented in vitro data in the published literature. Recognition of TKI resistance is important in CML, as the effect of some mutations can be overcome by increasing imatinib dosage, whereas others require switching to either a different (second-generation) TKI, or alternative therapy. The common T315I KD mutation is particularly important, given that this alteration confers pan-resistance to all currently employed TKIs except ponatinib. Typically, TKI resistance is suspected in a CML patient who shows loss of initial therapeutic response (eg, cytogenetic relapse), or a significant and sustained increase in molecular BCR-ABL1 quantitative levels. Similar considerations are also present in patients with Philadelphia chromosome positive B-cell acute lymphoblastic leukemia, who can also be treated using TKI therapy. Point mutations in the oncogenic BCR-ABL1 are typically detected by direct sequencing of PCR products, following RT-PCR amplification of the BCR-ABL mRNA transcript from a peripheral blood specimen. This approach ensures comprehensive screening of the clinically relevant KD region. Because this technique requires inclusion of a longer region of ABL1 in the BCR-ABL1 RT-PCR product, low levels of the BCR-ABL1 mRNA transcript (below 0.01% normalized BCR-ABL1 on the International Scale, IS) may not be efficiently amplified (in contrast to similar amplicons generated by quantitative RT-PCR for diagnosis or monitoring).

**Useful For:**
Evaluating patients with chronic myelogenous leukemia and Philadelphia chromosome positive B-cell acute lymphoblastic leukemia receiving tyrosine kinase inhibitor (TKI) therapy, who are apparently failing treatment. This is the preferred initial test to identify the presence of acquired BCR-ABL1 mutations associated with TKI-resistance.

**Interpretation:**
The presence of 1 or more point mutations in the translocated portion of the ABL1 region of the BCR-ABL1 fusion mRNA is considered a positive result, indicating tyrosine kinase inhibitor (TKI) resistance. The specific type of mutation may influence the sensitivity to a specific TKI, and could be useful in guiding therapeutic options for an individual patient.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Bean Black (Phaseolus spp) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Bean Coffee Green IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<23 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Bean Green/String IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Bean Kidney IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.
This test should only be ordered by physicians who recognize the limitations of the test.

**FBLME 57523**

**Bean Lima (Phaseolus limensis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 5 6 17.5 - 49.9 50.0 - 99.9 > or = 100 Very High Positive Very High Positive Very High Positive Very High Positive

**Reference Values:**

<0.35 kU/L

**FNBE 57937**

**Bean Navy/White (Phaseolus vulgaris) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal(Borderline) 1 0.35 – 0.69 Low Positive 2 0.70 – 3.4 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

**FBNWG 57655**

**Bean Navy/White IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**BWRS 35376**

**Beckwith-Wiedemann Syndrome (BWS)/Russell-Silver Syndrome (RSS) Molecular Analysis**

**Clinical Information:** Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Current data suggest that the etiology of BWS is due to dysregulation of imprinted genes in the 11p15 region of chromosome 11, including H19 (maternally expressed), LIT1 (official symbol KCNQ1OT1; paternally expressed), IGF2 (paternally expressed), and CDKN1C (aliases p57 and KIP2; maternally expressed). Expression of these genes is controlled by 2 imprinting centers (IC). Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is often due to inherited point mutations in CDKN1C or an unknown cause. The etiology of sporadic cases includes: -Hypomethylation of imprinting center 2 (IC2) (LIT1): approximately 50% to 60% -Paternal uniparental disomy of chromosome 11: approximately 10% to 20% -Hypermethylation of imprinting center 1 (IC1) (H19): approximately 2% to 7% -Unknown: approximately 10% to 20% -Point mutation in CDKN1C: approximately 5% to 10% -Cytogenetic abnormality: approximately 1% to 2% -Differentially methylated region 1 (DMR1) or DMR2

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The clinical presentation of BWS is dependent on which gene in the 11p15 region is involved. The risk for cancer has been shown to be significantly higher in patients with abnormal methylation of IC1 (H19) versus IC2 (LIT1). In patients with abnormal methylation of IC2 (LIT1), abdominal wall defects and overgrowth are seen at a higher frequency. Russell-Silver syndrome (RSS) is a rare genetic condition with an incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth retardation with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include cafe au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia. Although clinical diagnostic criteria have been developed, it has been demonstrated that many patients with molecularly confirmed RSS do not meet strict clinical diagnostic criteria for RSS. Therefore, most groups recommend a relatively low threshold for considering molecular testing in suspected cases of RSS. RSS is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes: - Hypomethylation of IC1 (H19): approximately 30% to 50% - Maternal uniparental disomy (UPD) of chromosome 7: approximately 5% to 10% - 11p15.5 duplications: rare - Chromosome 7 duplications: rare *Note that this test does not detect chromosome 7 UPD. However, testing is available; order UNIPD / Uniparental Disomy. The clinical phenotype of RSS has been associated with the specific underlying molecular etiology. Patients with hypomethylation of IC1 (H19) are more likely to exhibit “classic” RSS phenotype (i.e., severe intrauterine growth retardation, postnatal growth retardation, and asymmetry), while patients with maternal UPD7 often show a milder clinical phenotype. Despite these general genotype-phenotype correlations, many exceptions have been reported. Methylation abnormalities of IC1 (H19) and IC2 (LIT1) can be detected by methylation-sensitive multiple ligation-dependent probe amplification. While testing can determine methylation status, it does not identify the mechanism responsible for the methylation defect (such as paternal uniparental disomy or cytogenetic abnormalities). Hypomethylation of IC2 (LIT1) is hypothesized to silence the expression of a number of maternally expressed genes, including CDKN1C. Hypermethylation of IC1 is hypothesized to silence the expression of H19, while also resulting in overexpression of IGF2. Absence of CDKN1C and H19 expression, in addition to overexpression of IGF2, is postulated to contribute to the clinical phenotype of BWS. Hypomethylation of IC1 is hypothesized to result in overexpression of H19 and underexpression of the IGF2, which is thought to contribute to the clinical phenotype of RSS.

**Useful For:** Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome (BWS) or Russell-Silver syndrome (RSS) Prenatal diagnosis if there is a high suspicion of BWS/RSS based on ultrasound findings or in families at risk for BWS/RSS

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.


**Beech, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and...
clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FBEFG**

**Beef IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**BREG**

**Beef Neutral-Regular Insulin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergens that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Interpretation</th>
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</tr>
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<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders

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**BEEF 82697**

**Beef, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergens that may be associated with allergic disease. The allergens chosen for
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clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
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proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FBTRG 57689**

**Beet Root IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**BEETS 82618**

**Beets (Beetroot), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**FPHEN 91136** Benzene as Phenol, Occupational Exposure, Urine

**Reference Values:**
Creatinine: >50 mg/dL

 Phenol: mg/L
 Phenol: mg/G creat

 Normal (unexposed population): less than 10 mg/L

 Exposed:
 Biological Exposure Index (BEI): 50 mg/g creatinine (End of Shift)

 Toxic: Not Established

**FBEN 90294** Benzene, Occupational Exposure, Blood

**Reference Values:**
Units: mg/L

 Normal (unexposed population): None detected
 Exposed (end-of-shift): Blood benzene concentrations of greater than 0.1 mg/L correlate with exposure to greater than 10 ppm benzene in air.
 Toxic: Blood benzene concentrations greater than 0.90 mg/L have been observed in fatal cases of benzene exposure.
Benzodiazepines Confirmation, Chain of Custody, Urine

**Clinical Information:** Benzodiazepines are a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most commonly prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detecting drug use involving benzodiazepines such as alprazolam, flunitrazepam, chloridiazepoxide, diazepam, flurazepam, lorazepam, and triazolam Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: -Nordiazepam, oxazepam (metabolites of chloridiazepoxide) -Nordiazepam, oxazepam and temazepam (metabolites of diazepam) -Lorazepam -Hydroxyethylfluorazepam (metabolite of flurazepam) -Alpha hydroxyalprazolam (metabolite of alprazolam) -Alpha hydroxytriazolam (metabolite of triazolam) -7-Aminoflunitrazepam (metabolite of flunitrazepam) The clearance half-life of long-acting benzodiazepines is >24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5- to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Medical Laboratories Drugs of Abuse Testing Guide at http://www.mayomedicallaboratories.com/articles/drug-book/print-on-demand-select.php for additional information including metabolism, clearance (half-life), and approximate detection times.

**Reference Values:**
Negative
Cutoff concentrations:

**IMMUNOASSAY SCREEN**
<100 ng/mL

**NORDIAZEPAM BY GC-MS**
<100 ng/mL

**OXAZEPAM BY GC-MS**
<100 ng/mL

**LORAZEPAM BY GC-MS**
<100 ng/mL

**TEMAZEPAM BY GC-MS**
<100 ng/mL

**OH-ETHYL-FLURAZEPAM BY GC-MS**
<100 ng/mL

**7-NH-CLONAZEPAM BY GC-MS**
<100 ng/mL
Benzodiazepines Confirmation, Urine

Clinical Information: Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most commonly prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents.

Useful For: Detecting drug use involving benzodiazepines such as alprazolam, flunitrazepam, chlordiazepoxide, diazepam, flurazepam, lorazepam, and triazolam

Interpretation: Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: -Nordiazepam, oxazepam (metabolites of chlordiazepoxide) -Nordiazepam, oxazepam and temazepam (metabolites of diazepam) -Lorazepam -Hydroxyethylfluorazepam (metabolite of flurazepam) -Alpha hydroxyalprazolam (metabolite of alprazolam) -Alpha hydroxytriazolam (metabolite of triazolam) -7-aminoclonazepam (metabolite of clonazepam) -7-aminoflunitrazepam (metabolite of flunitrazepam) The clearance half-life of long-acting benzodiazepines is >24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5 to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Medical Laboratories Drugs of Abuse Testing Guide at http://www.mayomedicallaboratories.com/articles/drug-book/print-on-demand-select.php for additional information including metabolism, clearance (half-life), and approximate detection times.

Reference Values:

Negative

Cutoff concentrations:
NORDIAZEPAM BY GC-MS
<100 ng/mL

OXAZEPAM BY GC-MS
<100 ng/mL

LORAZEPAM BY GC-MS
<100 ng/mL

TEMAZEPAM BY GC-MS
<100 ng/mL

OH-ETHYL-FLURAZEPAM BY GC-MS
<100 ng/mL
7-NH-CLONAZEPAM BY GC-MS
<100 ng/mL

ALPHA OH-ALPRAZOLAM BY GC-MS
<100 ng/mL

7-NH-FLUNITRAZEPAM BY GC-MS
<50 ng/mL

ALPHA OH-TRIAZOLAM BY GC-MS
<100 ng/mL


FBENZ 90092
Benztropine (Cogentin), Serum
Reference Values:
Reference Range: 5.0 - 25.0 ng/mL

BBEET 82838
Berlin Beetle, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
BERG 82892

**Bermuda Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Class IgE kU/L</th>
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<td>0</td>
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<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Beryllium, Blood
Reference Values:
Reference Range: <1.0 ng/mL

Beta Lactoglobulin IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200
Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Beta-2 Glycoprotein 1 Antibodies, IgA, Serum
Clinical Information: Beta 2 glycoprotein 1 (beta 2 GP1, also called apolipoprotein H) is a 326 amino acid polypeptide synthesized by hepatocytes, endothelial cells and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta 2 GP1 antibodies that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with anti-phospholipid syndrome (APS). APS is associated with a variety of clinical symptoms notably thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livedo reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta 2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta 2 GP1 antibodies can be performed using either a composite substrate comprised of beta 2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta 2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta 2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as "beta 2 GP1 antibodies." Some beta 2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and laboratory criteria be met.(5) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placentation insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM antcardiolipin antibody (>40 GPL, >40 MPL or >99th percentile), and/or presence of IgG and/or IgM beta 2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta 2GP 1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(4) Anti-cardiolipin and beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.
Useful For: Evaluation of suspected cases of antiphospholipid syndrome

Interpretation: Strongly positive results for IgG and IgM beta 2 glycoprotein 1 (beta 2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta 2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Beta 2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA beta 2 GP1 antibody result >15 U/mL with negative IgG and IgM beta 2 GP1 antibody results are not diagnostic for APS. Detection of beta 2 GP1 antibodies is not affected by anticoagulant treatment.

Reference Values:
<10.0 U/mL (negative)
10.0-14.9 U/mL (borderline)
> or =15.0 U/mL (positive)
Results are expressed in arbitrary units.
Reference values apply to all ages.

Clinical References:
but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM anticardioplin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM beta 2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta 2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS. Anticardioplin and beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

**Useful For:** Evaluation of suspected cases of antiphospholipid syndrome

**Interpretation:** Strongly positive results for beta 2 glycoprotein 1 (beta 2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for APS. Lesser levels of beta 2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of antiphospholipid syndrome (APS), but the results are not considered diagnostic. Beta 2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta 2 GP1 antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <10.0 U/mL (negative)
- 10.0-14.9 U/mL (borderline)
- > or =15.0 U/mL (positive)

Results are expressed in arbitrary units and apply to IgG and IgM values.

Reference values apply to all ages.

**Clinical References:**

**Clinical Information:**

**Beta-2 Glycoprotein 1 Antibodies, IgG, Serum**

Beta 2 glycoprotein 1 (beta 2 GP1, also called apolipoprotein H) is a 326 amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each. Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta 2 GP1 (beta 2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with anti-phospholipid syndrome (APS). APS is associated with a variety of clinical symptoms notably thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livedo reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta 2 GP1 are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta 2 GP1 antibodies can be performed using either a composite substrate comprised of beta 2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta 2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta 2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as "beta 2 GP1 antibodies." Some beta 2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low
concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria to be met.(5) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >MPL or >99th percentile), and/or presence of IgG and/or IgM beta GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta 2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS (4). Anti-cardiolipin and beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of suspected cases of anti-phospholipid syndrome

Interpretation: Strongly positive results for beta 2 glycoprotein 1 (beta 2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for anti-phospholipid syndrome (APS). Lesser levels of IgG and IgM beta GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Beta 2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta 2 GP1 antibodies is not affected by anticoagulant treatment.

Reference Values:

- <10.0 U/mL (negative)
- 10.0-14.9 U/mL (borderline)
- > or =15.0 U/mL (positive)

Results are expressed in arbitrary units.

Reference values apply to all ages.

Clinical References:

Beta-2 Glycoprotein 1 Antibodies, IgM, Serum

Clinical Information: Beta 2 glycoprotein 1 (beta 2 GP1, also called apolipoprotein H) is a 326 amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta 2 GP1 (beta 2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms, notably, thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livedo reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta 2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta 2 GP1 antibodies can be performed using either a composite
substrate comprised of beta 2 GP1 plus anionic phospholipid (e.g., cardiolipin or phosphatidylserine), or beta 2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta 2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as "beta 2 GP1 antibodies." Some beta 2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM antiphospholipid antibody (>40 GPL, >40 MPL or >99th percentile), and/or presence of IgG and/or IgM beta 2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta 2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS. Anticardiolipin and beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of suspected cases of antiphospholipid syndrome

Interpretation: Strongly positive results for beta 2 glycoprotein 1 (beta 2 GPI) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta 2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Beta 2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta 2 GP1 antibodies is not affected by anticoagulant treatment.

Reference Values:
- <10.0 U/mL (negative)
- 10.0-14.9 U/mL (borderline)
- > or =15.0 U/mL (positive)
Results are expressed in arbitrary units.
Reference values apply to all ages.


Beta-2 Transferrin: Detection of Spinal Fluid in Other Body Fluid

Clinical Information: The diagnosis of cerebrospinal fluid (CSF) rhinorrhea or otorrhea (leakage of CSF into the nose or ear canal, usually as a result of head trauma, tumor, congenital malformation, or surgery) is often difficult to confirm. Traditional chemical analyses (e.g., glucose, protein, specific gravity) are unreliable. Radiographic studies, especially those involving the injection of dyes or radiographic compounds, are costly and may introduce additional risks to the patient. Transferrin that migrates in the beta-1 electrophoretic fraction (beta-1 transferrin) is found in most body fluids. Beta-2 transferrin is a CSF-specific variant of transferrin and is used as an endogenous marker of CSF leakage. Beta-2 transferrin is formed by loss of sialic acid due to the presence of neuraminidase in the central nervous system. Beta-2 transferrin has also been called CSF-specific transferrin and tau protein. Prompt diagnosis
and localization facilitates appropriate decisions and decreases the risk of meningitis.

**Useful For:** Detection of spinal fluid in body fluids, such as ear or nasal fluid

**Interpretation:** The cerebrospinal fluid (CSF) variant of transferrin is identified by its unique electrophoretic migration. If beta-1 and beta-2 transferrin are detected in drainage fluids, the specimen is presumed to be contaminated with CSF. The presence of beta-2 transferrin band is detectable with as little as 2.5% spinal fluid contamination of body fluids.

**Reference Values:**
Negative, no beta-2 transferrin (spinal fluid) detected

**Clinical References:**

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**Beta-2-Microglobulin (B-2-M), Spinal Fluid**

**Clinical Information:** Beta-2-microglobulin (B-2-M) is a small membrane protein (11,800 Dalton) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows B-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Increased B-2-M levels in the cerebrospinal fluid (CSF) have been shown to be of diagnostic use in non-Hodgkin lymphoma with central nervous system involvement. Elevated CSF:serum ratios seen in patients with aseptic meningoc-encephalitis suggest the possibility of neurologic processes including those associated with HIV infection and acute lymphoblastic leukemia. B-2-M measurement in multiple sclerosis seems to be of indeterminate usefulness.

**Useful For:** Evaluation of central nervous system inflammation and B-cell proliferative diseases

**Interpretation:** Elevations of cerebrospinal fluid beta-2-microglobulin levels may be seen in a number of diseases including malignancies, autoimmune disease, and neurological disorders.

**Reference Values:**
0.70-1.80 mcg/mL

**Clinical References:**
**Clinical Information:** Beta-2-microglobulin (beta-2-M) is a small membrane protein (11,800 Dalton) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows beta-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Serum beta-2-M levels are elevated in diseases associated with increased cell turnover. Levels are also elevated in several benign conditions such as chronic inflammation, liver disease, renal dysfunction, some acute viral infections, and a number of malignancies, especially hematologic malignancies associated with the B-lymphocyte lineage. In multiple myeloma, beta-2-M is a powerful prognostic factor and values <4 mcg/mL are considered a good prognostic factor. In renal tubular disease, serum levels are low and urine levels are high. Although urine beta-2-M has been used to assess tubular dysfunction, it is not stable in urine below pH 5.5. See Diagnosis and Monitoring of Multiple Myeloma in Publications. Also see Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Prognosis assessment of multiple myeloma Evaluation of renal tubular disorders

**Interpretation:** Serum beta-2-microglobulin (beta-2-M) <4 mcg/mL is a good prognostic factor in patients with multiple myeloma. In a study of pretreatment serum beta-2-M levels in 100 patients with myeloma it was reported that the median survival of patients with values >4 mcg/mL was 12 months, whereas median survival for patients with values <4 mcg/mL was 43 months.

**Reference Values:**
1.21-2.70 mcg/mL

**Clinical References:**

**FB2MU**  
Beta-2-Microglobulin, Urine

**Reference Values:**
Beta-2-Microglobulin, Urine : 0 - 300  g/L  
Beta-2-Microglobulin, ratio to CRT: 0 - 300  g/g CRT

**BCARO**  
Beta-Carotene, Serum

**Clinical Information:** Beta-carotene is a member of the family of carotenoids, highly pigmented (red, orange, yellow) fat-soluble vitamins that are the precursors or provitamins of vitamin A. The principle provitamin A compounds include beta-carotene, alpha-carotene, and beta-cryptoxanthin. Carotenoids occur in high levels in many fruits and vegetables such as carrots, sweet potatoes, cantaloupe, and others. The most significant effect of these provitamins is their conversion to vitamin A, which plays a major role in vision as well as reproduction, embryonic growth, and immune function. The highest levels of carotene can be found in the serum of individuals ingesting large amounts of vegetables, primarily carrots. These people may have a slight yellowish tinge of the skin but the sclera of the eye is not discolored. Decreased serum levels may be seen in individuals with nutritional deficiencies including anorexia nervosa, malabsorption, and steatorrhea.

**Useful For:** Detection of a nutritional deficiency of carotene Detection of excessive ingestion of carotene

**Interpretation:** Low beta-carotene concentrations in the serum are indicative of vitamin insufficiency.
Elevated levels of beta-carotene may have clinical implications.

**Reference Values:**
> or =18 years: 2.3-65.0 mcg/dL  
<18 years: not established

**Clinical References:** 1. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000 pp 325-382  

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**BCAT**

**Beta-Catenin, Fibromatosis, Mutation Analysis**

**Clinical Information:** Desmoid-type fibromatosis is a locally invasive soft tissue tumor. The histological diagnosis of desmoid-type fibromatosis is challenging. Mutations in exon 3 of the beta-catenin gene have been identified in 50% to 87% of desmoid-type fibromatosis, including T41A (121 A->G), S45P (133 T->C), and S45F (134 C->T), but not in other soft tissue tumors. Patients harboring beta-catenin mutations may have a higher recurrence rate compared to the patients with wild-type beta-catenin.

**Useful For:** Distinguishing desmoid-type fibromatosis from other soft tissue tumors, when pathological examination is insufficient for diagnosis

**Interpretation:** Beta-catenin mutations are detected using PCR and pyrosequencing methods. The mutant allele frequencies (%) are used to determine beta-catenin mutation status. Results are reported as positive, negative, or failed. A beta-catenin mutation-positive result supports a diagnosis of desmoid-type fibromatosis, but a negative result does not necessarily rule out a diagnosis of desmoid-type fibromatosis.

**Reference Values:**
An interpretative report will be provided.


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**CTX**

**Beta-CrossLaps (Beta-CTx), Serum**

**Clinical Information:** Human bone is continuously remodeled through a process of bone formation and resorption. Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is crosslinked at the N- and C-terminal ends of the molecule. During bone resorption, osteoclasts secrete a mixture of acid and neutral proteases that degrade the collagen fibrils into molecular fragments including C-terminal telopeptide (CTx). As bone ages, the alpha form of aspartic acid present in CTx converts to the beta form (beta-CTx). Beta-CTx is released into the bloodstream during bone resorption and serves as a specific marker for the degradation of mature type I collagen. Elevated serum concentrations of beta-CTx have been reported in patients with increased bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and are of no diagnostic value. By contrast, bone turnover markers may be useful when the bone remodeling process is unbalanced.
Abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget’s disease, multiple myeloma, and bone metastases, as well as various congenital diseases of bone formation and remodeling, can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption markers.

**Useful For:** An aid in monitoring antiresorptive therapies (e.g., bisphosphonates and hormone replacement therapy) in postmenopausal women treated for osteoporosis and individuals diagnosed with osteopenia. An adjunct in the diagnosis of medical conditions associated with increased bone turnover.

**Interpretation:** Elevated levels of beta-CTx indicate increased bone resorption. Increased levels are associated with osteoporosis, osteopenia, Paget’s disease, hyperthyroidism, and hyperparathyroidism. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy), a decrease of > or =25% from baseline beta-CTx levels (i.e., prior to the start of therapy) 3 to 6 months after initiation of therapy indicates an adequate therapeutic response.

**Reference Values:**

**Males**
- <18 years: not established
- 18-30 years: 155-873 pg/mL
- 31-50 years: 93-630 pg/mL
- 51-70 years: 35-836 pg/mL
- >70 years: not established

**Females**
- <18 years: not established
- Premenopausal: 25-573 pg/mL
- Postmenopausal: 104-1,008 pg/mL

**Clinical References:**

**Beta-Galactosidase, Blood**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. The deficiency of this enzyme can lead to the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years presenting with developmental delays and a slower progression. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Mucopolysaccharidosis type IVB (MPS IVB, Morquio B) is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAGs). Accumulation of GAGs (also known as mucopolysaccharides) in...
lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB is caused by a reduced or absent activity of the beta-galactosidase enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Treatment options are limited to symptomatic management. Galactosialidosis is an autosomal recessive lysosomal storage disease associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death. The late infantile form typically presents with short stature dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and/or heart valve problems. The juvenile/adult form is typically characterized by progressive neurologic degeneration, ataxia, and/or angiokeratomas. The incidence of the juvenile/adult form is greater in individuals with Japanese ancestry. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes and/or fibroblasts; however, enzymatic testing is not reliable to detect carriers. Individuals with galactosialidosis would also have decreased neuraminidase activity in leukocytes and/or fibroblasts in addition to decreased beta-galactosidase enzyme activity. Molecular sequence analysis of the GLB1 gene allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis and/or Morquio B and sequencing of the CTSA gene allows for detection of disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of GM1 gangliosidosis, Morquio B disease, and galactosialidosis

**Interpretation:** Results <5.0 nmol/h/mL in properly submitted specimens are consistent with beta-galactosidase deficiency (GM1 gangliosidosis and Morquio B disease). Further differentiation between GM1 and Morquio B is dependent on the patient's clinical findings. Normal results (≥ or =5.0 nmol/h/mL) are not consistent with beta-galactosidase deficiency.

**Reference Values:**

≥ or =5.0 nmol/h/mL

An interpretive report will be provided.

**Clinical References:**

Accumulation of GAGs (also known as mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB is caused by a reduced or absent activity of the beta-galactosidase enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Treatment options are limited to symptomatic management. Galactosialidosis is an autosomal recessive lysosomal storage disease associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death. The late infantile form typically presents with short stature dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and/or heart valve problems. The juvenile/adult form is typically characterized by progressive neurologic degeneration, ataxia, and/or angiokeratomas. The incidence of the juvenile/adult form is greater in individuals with Japanese ancestry. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes and/or fibroblasts; however, enzymatic testing is not reliable to detect carriers. Individuals with galactosialidosis would also have decreased neuraminidase activity in leukocytes and/or fibroblasts in addition to decreased beta-galactosidase enzyme activity. Molecular sequence analysis of the GLB1 gene allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis and/or Morquio B and sequencing of the CTSA gene allows for detection of disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of beta-galactosidase deficiency (GM1 gangliosidosis and Morquio B disease) and galactosialidosis

**Interpretation:** Properly submitted specimens with results <5.0 nmol/h/mL are consistent with beta-galactosidase deficiency (GM1 gangliosidosis and Morquio B disease). Further differentiation between GM1 and Morquio B is dependent on the patient’s clinical findings. Normal results (≥ 5.0 nmol/h/mL) are not consistent with beta-galactosidase deficiency.

**Reference Values:**

- or = 5.0 nmol/h/mL

An interpretive report will be provided.

**Clinical References:**

**Beta-Galactosidase, Fibroblasts**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of beta-galactosides. A deficiency of this enzyme is implicated in the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years and presenting with developmental delays or regression and a slower clinical course. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Morquio B (MPS IVB) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent beta-galactosidase activity.
resulting in the accumulation of keratan sulfate in the lysosomes. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Treatment options are limited to symptomatic management. Galactosialidosis is an autosomal recessive lysosomal storage disease (LSD) associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. Clinical features are those typically associated with LSDs including coarse facial features, cherry-red spots, and/or skeletal dysplasia. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal and ophthalmologic disorders, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features, hepatosplenomegaly, and/or heart valve problems. The juvenile/adult form is characterized by progressive neurologic degeneration, ataxia, cognitive disability, and/or angiokeratomas. Most of the juvenile/adult form cases have been found in individuals with Japanese ancestry. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes and/or fibroblasts, however, individuals with galactosialidosis would also have decreased neuraminidase activity in leukocytes and/or fibroblasts. Enzymatic testing is not reliable to detect carriers. Molecular sequence analysis of GLB1 allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis and/or Morquio B, and sequencing of CTSA allows for detection of disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis

**Interpretation:** Beta-galactosidase is deficient in GM1 gangliosidosis and Morquio syndrome B. The deficiency of beta-galactosidase combined with neuraminidase deficiency is characteristic of galactosialidosis.

**Reference Values:**
> or =7.11 nmol/min/mg protein

**Clinical References:**

**Beta-Galactosidase, Leukocytes**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. The deficiency of this enzyme can lead to the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7
months and 3 years and presenting with developmental delays or regression and a slower clinical course. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Morquio B (MPS IVB) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent beta-galactosidase activity resulting in the accumulation of keratan sulfate in the lysosomes. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Treatment options are limited to symptomatic management.

Galactosialidosis is an autosomal recessive lysosomal storage disease (LSD) associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. Clinical features are those typically associated with LSDs including coarse facial features, cherry-red spots, or skeletal dysplasia. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal and ophthalmologic disorders, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features, hepatosplenomegaly, and/or heart valve problems. The juvenile/adult form is characterized by progressive neurologic degeneration, ataxia, cognitive disability, and/or angio keras tomas. Most of the juvenile/adult form cases have been found in individuals with Japanese ancestry. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes and/or fibroblasts; however, individuals with galactosialidosis would also have decreased neuraminidase activity in leukocytes and/or fibroblasts. Enzymatic testing is not reliable to detect carriers. Molecular sequence analysis of the GLB1 gene allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis and/or Morquio B and sequencing of the CTSA gene allows for detection of disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of GM1 gangliosidosis, Morquio B disease, and galactosialidosis

**Interpretation:** Very low enzyme activity levels are consistent with GM1 gangliosidosis and Morquio B disease. Clinical findings must be used to differentiate between those 2 diseases. The deficiency of beta-galactosidase combined with neuraminidase deficiency (see NEURF / Neuraminidase, Fibroblasts) is characteristic of galactosialidosis.

**Reference Values:**

> or =1.56 nmol/min/mg

**Clinical References:**
variable within Gaucher disease, but in general, the disorder is characterized by bone disease, hepatosplenomegaly, and may have central nervous system (CNS) involvement. There are 3 clinical subtypes of the disorder that vary with respect to age of onset and clinical presentation. Type 1 is the most common type, representing 95% of all cases, and is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, and no CNS involvement. Type 2 typically has a very severe progression with onset prior to 2 years, with neurologic disease, hepatosplenomegaly, and lung disease, with death usually between 2 and 4 years due to lung failure. Individuals with type 3 may have onset prior to 2 years of age, but the progression is not as severe and they may survive into the third and fourth decade. In addition, there is a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Treatment is available in the form of enzyme replacement therapy and/or substrate reduction therapy for types 1 and 3. Individuals with type 3 may benefit from bone marrow transplantation. Currently, only supportive therapy is available for type 2. The incidence of type 1 ranges from 1 in 20,000 to 1 in 200,000 in the general population, but is much more frequent among Ashkenazi Jews with an incidence ranging from 1 in 400 to 1 in 900. Types 2 and 3 both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic work up for Gaucher disease may demonstrate the characteristic finding of "Gaucher cells" on bone marrow examination. Reduced or absent enzyme activity of acid beta-glucosidase is diagnostic. A targeted mutation panel may allow for detection of disease-causing mutations in affected patients (GAUP / Gaucher Disease, Mutation Analysis, GBA). In addition, full sequencing of GBA (GBAZ / Gaucher Disease, Full Gene Analysis) allows for detection of disease-causing mutations in affected patients for whom a targeted mutation panel identifies a single or no mutation.

**Useful For:** Diagnosis of Gaucher disease

**Interpretation:** Marked deficiency of acid beta-glucosidase is consistent with a diagnosis of Gaucher disease.

**Reference Values:**

\[ > \text{or} = 4.85 \, \text{nmol/min/mg protein} \]

**Clinical References:**


**Beta-Glucosidase, Leukocytes**

**Clinical Information:** Gaucher disease is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid beta-glucosidase (glucocerebrosidase) enzyme activity. Absent or reduced activity of this enzyme results in accumulation of glucocerebroside in the lysosomes and interferes with the normal functioning of cells. Clinical features and severity of symptoms are widely variable within Gaucher disease, but in general, the disorder is characterized by abnormal blood parameters such as decreased red blood cells (anemia) and/or platelets (thrombocytopenia), bone disease, and hepatosplenomegaly. Individuals with more severe types of Gaucher disease may have central nervous system (CNS) involvement. There are 3 clinical subtypes of the disorder that vary with respect to age of onset and clinical presentation. Type 1 is the most common type, representing 95% of all cases, and is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, and no CNS involvement. Type 2 typically has a very severe progression with onset in the first 2 years of life including neurologic disease, hepatosplenomegaly, and lung disease, with death usually between 2 and 4 years due to lung failure. Individuals with type 3 may have onset prior to 2 years of age, but the progression is not as severe and they may survive into the third and fourth decade. In
addition, there is a perinatal lethal form associated with skin abnormalities and nonimmune hydrops feticis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and/or chaperone therapy for types 1 and 3. Individuals with type 3 may benefit from bone marrow transplantation. Currently, only supportive therapy is available for type 2. The incidence of type 1 ranges from 1 in 20,000 to 200,000 in the general population, but is much more frequent among Ashkenazi Jews with an incidence between 1 in 400 and 900. Types 2 and 3 both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of "Gaucher cells" on bone marrow examination. Reduced or absent enzyme activity of acid beta-glucosidase is diagnostic. A targeted mutation panel may allow for detection of disease-causing mutations in affected patients (GAUP / Gaucher Disease, Mutation Analysis, GBA). In addition, full sequencing of the GBA gene allows for detection of disease-causing mutations in affected patients in whom a targeted mutation panel identifies only a single mutation (GBAZ / Gaucher Disease, Full Gene Analysis).

**Useful For:** Diagnosis of Gaucher disease

**Interpretation:** Values <8.7 nmol/h/mg protein are consistent with a diagnosis of Gaucher disease.

**Reference Values:**

> or =8.7 nmol/h/mg protein

Note: Results from this assay do not reflect carrier status because of individual variation of beta-glucosidase enzyme levels. For carrier testing, order molecular test GAUP / Gaucher Disease, Mutation Analysis, GBA.

**Clinical References:**


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**BGLR 8006**

**Beta-Glucuronidase, Fibroblasts**

**Clinical Information:** Mucopolysaccharidosis VII (MPS VII, Sly syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of beta-glucuronidase. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of glycosaminoglycans (GAG). Accumulation of GAGs (also called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS VII is caused by a reduced or absent activity of the beta-glucuronidase enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS VII are widely variable ranging from severe lethal hydrops feticis to more mild forms, which generally present at a later onset with a milder clinical presentation. In general, symptoms may include skeletal anomalies, coarse facies, hepatomegaly, neurological issues, and mental retardation. Treatment options may include bone marrow transplantation. Sly syndrome is 1 of the least common mucopolysaccharidoses with an incidence of 1 in 250,000 live births. A diagnostic workup in an individual with MPS VII typically demonstrates elevated levels of urinary GAGs and increased amounts of dermatan sulfate, heparan sulfate, and chondroitin 6-sulfate detected on thin-layer chromatography. Reduced or absent activity of beta-glucuronidase in fibroblasts can confirm a diagnosis of MPS VII; however, enzymatic testing is not reliable to detect carriers. Molecular sequence analysis of the GUSB gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in relatives. Currently, no clear genotype-phenotype correlations have been established.

**Useful For:** Detection of mucopolysaccharidosis type VII
**BHCG 61718**

**Beta-Human Chorionic Gonadotropin, Quantitative, Serum**

**Clinical Information:** Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight [MW] approximately 36,000 Dalton [Da]) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyroid-stimulating hormone (TSH). The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da, glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans) it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. hCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in particular seminomatous and nonseminomatous testicular tumors; ovarian germ cell tumors; gestational trophoblastic disease (GTD: hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including this assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours, and eventually return to the reference range.

**Useful For:** Monitoring patients for retained products of conception An aid in the diagnosis of gestational trophoblastic disease (GTD), testicular tumors, ovarian germ cell tumors, teratomas, and, rarely, other human chorionic gonadotropin (hCG)-secreting tumors Serial measurement of hCG following treatment to: -Monitor therapeutic response in GTD or in hCG-secreting tumors -Detect persistent or recurrent GTD or hCG-secreting tumors

**Interpretation:** After delivery, miscarriage, or pregnancy termination, human chorionic gonadotropin (hCG) falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. An absent or significantly slower decline is seen in patients with retained products of conception. Gestational trophoblastic disease (GTD) is associated with very considerable elevations of hCG, usually above 2 multiples of the medians for gestational age persisting or even rising beyond the first trimester. Serum hCG levels are elevated in approximately 40% to 50% of patients with nonseminomatous testicular cancer and 20% to 40% of patients with seminoma. Markedly elevated levels of hCG (>5,000 IU/L) are uncommon in patients with pure seminoma and indicate the presence of a mixed testicular cancer. Ovarian germ cell tumors (approximately 10% of ovarian tumors) display elevated hCG levels in 20% to 50% of cases. Teratomas in children may overproduce hCG, even when benign, resulting in precocious pseudopuberty. Levels may be elevated to similar levels as seen in testicular cancer. Among nonreproductive tumors, hepatobiliary tumors (hepatoblastomas, hepatocellular carcinomas, and cholangiocarcinomas) and neuroendocrine tumors (eg, islet cell tumors and carcinoids) are those most
commonly associated with hCG production. Many hCG-producing tumors also produce other embryonic proteins or antigens, in particular alpha fetoprotein (AFP). AFP should, therefore, also be measured in the diagnostic workup of such neoplasms. Complete therapeutic response in hCG-secreting tumors is characterized by a decline in hCG levels with an apparent half-life of 24 to 36 hours and eventual return to concentrations within the reference range. GTD and some tumors may produce hyperglycosylated hCG with a longer half-life, but an apparent half-life of >3 days suggests the presence of residual hCG-producing tumor tissue. A rise in hCG levels above the reference range in patients with hCG-producing tumors that had previously been treated successfully, suggests possible local or distant metastatic recurrence.

**Reference Values:**

**Children**(1,2)

**Males**
- Birth-3 months: < or = 50 IU/L*
- >3 months-<18 years: <1.4 IU/L

**Females**
- Birth-3 months: < or = 50 IU/L*
- >3 months-<18 years: <1.0 IU/L

*hCG, produced in the placenta, partially passes the placental barrier. Newborn serum beta-hCG concentrations are approximately 1/400th of the corresponding maternal serum concentrations, resulting in neonate beta-hCG levels of 10-50 IU/L at birth. Clearance half-life is approximately 2-3 days. Therefore, by 3 months of age, levels comparable to adults should be reached.

**Adults** (97.5th percentile)

**Males:** <1.4 IU/L

**Females**
- Premenopausal, nonpregnant: <1.0 IU/L
- Postmenopausal: <7.0 IU/L

Pediatric reference values based on:


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**Beta-Human Chorionic Gonadotropin, Quantitative, Spinal Fluid**

**Clinical Information:** Human chorionic gonadotropin (hCG) is synthesized during pregnancy by syncytiotrophoblast cells. hCG may also be produced by neoplastic cells of testicular tumors (seminomas or nonseminomas), ovarian germ cell tumors, gestational trophoblastic disease, choriocarcinoma and various nontrophoblastic tumors, including breast, ovarian, pancreatic, cervical, gastric, and hepatic cancers. Measurement of hCG is used as an adjunct in the diagnosis of germ cell tumors. The presence of hCG in cerebrospinal fluid (CSF) is suggestive of tumor presence. Pure germinomas are associated with low hCG concentrations in both serum and CSF. A subset of nongerminomatous germ cell tumors contains syncytiotrophoblastic giant cells. These tumors are associated with moderately increased hCG concentrations (<1000 IU/L) in the serum and/or CSF, and the survival rate in patients suffering these
tumors is worse than that of patients with pure germinomas. In contrast, choriocarcinomas, another subset of nongerminomatus germ cell tumors, are associated with very high hCG concentrations (>1000 IU/L) in both serum and CSF. Quantification of the hCG in CSF can be important in guiding treatment and monitoring response to treatment of these tumors. The combination of the specific antibodies used in the Roche Beta HCG immunoassay recognize the holo-hormone, "nicked" forms of hCG, the beta-core fragment, and the free beta-subunit.

**Useful For:** As an aid in the diagnosis of brain metastases of testicular cancer or extragonadal intracerebral germ cell tumors

**Interpretation:** Elevated levels of human chorionic gonadotropin in spinal fluid indicate the probable presence of central nervous system metastases or recurrence of tumor in patients with germ cell tumors, including patients with testicular cancer or choriocarcinoma.

**Reference Values:**

<1.0 IU/L

**Clinical References:**


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**Beta-Hydroxybutyrate, Serum**

**Clinical Information:** Beta-hydroxybutyrate (BHB) is 1 of 3 sources of ketone bodies. Its relative proportion in the blood (78%) is greater than the other 2 ketone bodies, acetoacetate (20%) and acetone (2%). During carbohydrate deprivation (starvation, digestive disturbances, frequent vomiting), decreased carbohydrate utilization (diabetes mellitus), glycogen storage diseases, and alkalosis, acetoacetate production increases. The increase may exceed the metabolic capacity of the peripheral tissues. As acetoacetate accumulates in the blood, a small amount is converted to acetone by spontaneous decarboxylation. The remaining and greater portion of acetoacetate is converted to BHB.

**Useful For:** Monitoring therapy for diabetic ketoacidosis Investigating the differential diagnosis of any patient presenting to the emergency room with hypoglycemia, acidosis, suspected alcohol ingestion, or an unexplained increase in the anion gap In pediatric patients, the presence or absence of ketonemia/uria is an essential component in the differential diagnosis of inborn errors of metabolism Serum beta-hydroxybutyrate is a key parameter monitored during controlled 24-hour fasts

**Interpretation:** The beta-hydroxybutyrate (BHB)/acetoacetate ratio is typically between 3:1 and 7:1 in severe ketotic states. Serum BHB increases in response to fasting, but should not exceed 0.4 mmol/L following an overnight fast (up to 12 hours). In pediatric patients, a hypo- or hyper-ketotic state (with or without hypoglycemia) may suggest specific groups of metabolic disorders.

**Reference Values:**

<0.4 mmol/L

**Clinical References:**


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**Beta-Lactamase**

**Clinical Information:** Various bacteria produce a class of enzymes called beta-lactamases, which
may be mediated by genes on plasmids or chromosomes. Production of beta-lactamase may be constitutive or induced by exposure to antimicrobials. Beta-lactamases hydrolyze (and thereby inactivate) the beta-lactam rings of a variety of susceptible penicillins and cephalosporins. Beta-lactamases are classified by their preferred antimicrobial substrate and the effect of various inhibitors (such as clavulanic acid) on them. Some antimicrobials, such as cefazolin and cloxacillin are resistant to such hydrolysis (at least for staphylococcal beta-lactamases). Beta-lactamase producing strains of the following are resistant to many types of penicillin: Staphylococcus species, Hemophilus influenzae, Neisseria gonorrhoeae, Bacteroides species, Enterococcus species, and Moraxella catarrhalis. The above organisms, when isolated from critical specimens such as blood or spinal fluid, should always be tested for beta-lactamase production. Addition of a beta-lactamase inhibitor to a beta-lactam (such as sulbactam plus ampicillin) restores the activity of the antimicrobials.

Useful For: Predicting the resistance of beta-lactamase producing isolates to hydrolysis-susceptible beta-lactam antimicrobials

Interpretation: A positive test indicates production of beta-lactamase.

Reference Values:
Negative (reported as positive or negative)


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**Beta-Lactoglobulin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Bicarbonate, Serum**

**Clinical Information:** Bicarbonate is the second largest fraction of the anions in plasma. Included in this fraction are the bicarbonate (HCO$_3^-$) and carbonate (CO$_3^{2-}$) ions, carbon dioxide in physical solution, as well as the carbamino compounds. At the physiological pH of blood, the concentration of carbonate is 1/1000 that of bicarbonate. The carbamino compounds are also present in such low quantities that they are generally not mentioned specifically.

**Useful For:** The bicarbonate content of serum or plasma is a significant indicator of electrolyte dispersion and anion deficit. Together with pH determination, bicarbonate measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with acid-base imbalance in the respiratory and metabolic systems. Some of these conditions are diarrhea, renal tubular acidosis, carbonic anhydrase inhibitors, hyperkalemic acidosis, renal failure, and ketoacidosis.

**Interpretation:** Alterations of bicarbonate and CO$_2$ dissolved in plasma are characteristic of acid-base imbalance. The nature of the imbalance cannot, however, be inferred from the bicarbonate value itself, and the determination of bicarbonate is rarely ordered alone. Its value has significance in the context of other electrolytes determined with it and in screening for electrolyte imbalance.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>12-24 months: 17-25 mmol/L</td>
</tr>
<tr>
<td></td>
<td>3 years: 18-26 mmol/L</td>
</tr>
<tr>
<td></td>
<td>4-5 years: 19-27 mmol/L</td>
</tr>
<tr>
<td></td>
<td>6-7 years: 20-28 mmol/L</td>
</tr>
<tr>
<td></td>
<td>8-17 years: 21-29 mmol/L</td>
</tr>
<tr>
<td></td>
<td>&gt; or =18 years: 22-29 mmol/L</td>
</tr>
<tr>
<td>Females</td>
<td>1-3 years: 18-25 mmol/L</td>
</tr>
<tr>
<td></td>
<td>4-5 years: 19-26 mmol/L</td>
</tr>
<tr>
<td></td>
<td>6-7 years: 20-27 mmol/L</td>
</tr>
<tr>
<td></td>
<td>8-9 years: 21-28 mmol/L</td>
</tr>
<tr>
<td></td>
<td>&gt; or =10 years: 22-29 mmol/L</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are <12 months of age.


**Bicarbonate, Urine**

**Reference Values:**

Reporting limit determined each analysis.

<table>
<thead>
<tr>
<th>Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normally</td>
<td>None Detected</td>
</tr>
<tr>
<td>Units</td>
<td>molar</td>
</tr>
</tbody>
</table>
Bile Acids, Fractionated and Total, 48 Hour, Feces

Clinical Information: Bile acids are natural products of cholesterol synthesis that aid in the emulsification and absorption of dietary fats in the small intestine. The majority of bile acids are reabsorbed in the ileum of the healthy individual, with only 5% secreted in feces. Primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are deconjugated and dehydroxylated via intestinal bacteria into secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. The sum of CA, CDCA, DCA, LCA, and ursodeoxycholic acid (UDCA) compose the majority of bile acids in the feces. Impaired absorption of bile acids in the terminal ileum leads to excess bile acids in the colon that can cause diarrhea from chloride and water secretion; a condition called bile acid malabsorption (BAM). Irritable bowel syndrome (IBS) is a nonspecific multifactorial disorder involving the large intestine. IBS is characterized by cramping, bloating, diarrhea, and constipation and classified as either IBS-D (diarrhea) or IBS-C (constipation) by the Rome III criteria. Up to 50% of IBS-D patients have accelerated colonic transit time; the mechanism of IBS-D pathophysiology is varied with more than 25% having BAM. Several methods have been developed for detection of BAM but are not widely available in clinical practice. Therefore, patients are often placed on trials of bile acids sequestrants to determine if symptoms improve. Quantitation of fecal bile acids aids in screening for IBS-D and identification of patients with chronic diarrhea who may benefit from bile acid sequestrant therapy.

Useful For: An aid to evaluate patients suspected of having irritable bowel syndrome-diarrhea (IBS-D) symptoms due to bile acid malabsorption

Interpretation: Elevated total fecal bile acid is consistent with the diagnosis of bile acid malabsorption. Pharmacological treatment with bile acid sequestrants has been shown to improve symptoms in some patients.

Reference Values:
Sum of cholic acid and chenodeoxycholic acid < or =3.7%
Total bile acids < or =2,619 mcmoles/48 hours


Bile Acids, Fractionated and Total, Serum

Clinical Information: Bile acids can be elevated in individuals with liver dysfunction, such as hepatitis, cirrhosis, liver sclerosis, liver cancer, and intrahepatic cholestasis of pregnancy.

Useful For: Measurement of tauro- and glycol-conjugated and unconjugated bile acid constituents in serum May also be useful for monitoring patients receiving bile acid therapy, such as cholic acid, deoxycholic acid, or ursodeoxycholic acid

Interpretation: Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum bile acids are seen in patients with acute hepatitis, chronic hepatitis, liver sclerosis, liver cancer, and intrahepatic cholestasis of pregnancy.

Reference Values:
Analyte Normal (nmol/mL)
Total Cholic Acid < or =5.00
Total Chenodeoxycholic Acid < or =6.00
Total Deoxycholic Acid < or =6.00
Total Ursodeoxycholic Acid < or =2.00
Total Bile Acids < or =19.00


FFBAT 75159 Bile Acids, Total
Reference Values:
0 â€“ 10 umol/L

84357 Biliary Tract Malignancy, Cytology and Molecular Testing
Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (eg, aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for malignancy
Interpretation: An interpretive report will be provided.
Reference Values:
An interpretive report will be provided.


19701 Biliary Tract Malignancy, FISH Only
Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (eg, aneuploidy)
that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

**Useful For:** Assessing bile duct brushing or hepatobiliary brushing specimens for malignancy

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Bilirubin Direct, Serum**

**Clinical Information:** Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin while the remaining 15% is produced from the RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. Direct bilirubin is a measurement of conjugated bilirubin. Jaundice can occur as a result of problems at each step in the metabolic pathway. Disorders may be classified as those due to: increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). Inherited disorders in which direct bilirubinemia occurs include Dubin-Johnson syndrome and Rotor Syndrome. Jaundice of the newborn where direct bilirubin is elevated includes idiopathic neonatal hepatitis and biliary atresia. The most commonly occurring form of jaundice of the newborn, physiological jaundice, results in unconjugated (indirect) hyperbilirubinemia. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The increased production of bilirubin that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage and excretion are impaired to varying degrees. Thus both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatocellular diseases, such as hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Evaluation of jaundice and liver functions

**Interpretation:** Direct bilirubin levels must be assessed in conjunction with total and indirect levels and the clinical setting.

**Reference Values:**
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

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**Bilirubin, Amniotic Fluid**

**Clinical Information:** The presence of bilirubin in amniotic fluid, which results in a yellow color, is an indicator of fetal erythroblastosis. Visual inspection of amniotic fluid is unreliable because bilirubin is not the only cause of an excessive yellow color; therefore, the presence of bilirubin must be confirmed...
with spectrophotometric methods. Meconium may contribute a green color (biliverdin) that can obscure the color of bilirubin and hemoglobin.

**Useful For:** Evaluation of Rh disease, ie, hemolytic disease of the fetus Monitoring disease progression to assess need for fetal transfusion

**Interpretation:** The reference range for bilirubin in amniotic fluid is related to the gestational age of the fetus. Refer to either the Queenan Curve (gestational age <27 weeks) or the Liley Chart (gestational age >27 weeks) listed under Interpretation of Amniotic Fluid Bilirubin Results (Delta OD 450) in Special Instructions.

**Reference Values:**
Interpretation of fetal risk is dependent upon gestational age.
Refer to either the Queenan Curve (gestational age <27 weeks) or the Liley Chart (gestational age >27 weeks) listed under Interpretation of Amniotic Fluid Bilirubin Results (Delta OD 450) in Special Instructions.

**Clinical References:**
1. Scott F, Chan FY: Assessment of the clinical usefulness of the 'Queenan' chart versus the 'Liley' chart in predicting severity of rhesus iso-immunization. Prenat Dia gn 1998;18:1143-1148

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**Bilirubin, Body Fluid**

**Clinical Information:** Assessing whether a body fluid specimen is exudative or transudative in nature is the initial step in determining the etiology of the fluid. Transudative fluids result from hemodynamic aberrations or oncotic changes and are associated with ultrafiltration of serum across pleural membranes. Transudates most commonly occur in association with clinically apparent conditions such as heart failure and cirrhosis. Exudative fluids tend to develop as a consequence of inflammation or malignant disorders such as tuberculosis, pneumonia, or cancer, in which capillary permeability is increased, allowing large-molecular-weight compounds to be released into the accumulating fluid. If the fluid is transudate, further diagnostic procedures are often not necessary, however the presence of an exudative fluid often triggers additional testing that may be invasive in nature. Determination of body fluid bilirubin concentration can aid in the distinction between a transudative and an exudative fluid. Bilirubin values tend to be higher in exudates than in transudates, although there is some overlap between groups. However, a ratio of body fluids to serum bilirubin has been reported to identify exudative body fluids with sensitivity, specifically, positive predictive accuracy, and absolute accuracy equivalent to that obtained using Light's criteria for an exudative pleural fluid (pleural/serum protein ratio >0.5, pleural/serum lactate dehydrogenase ratio >0.6, and serum lactate dehydrogenase >200 U/L).

**Useful For:** May aid in the distinction between a transudative and an exudative body fluid, when used in conjunction with other testing including serum bilirubin analysis, body fluid:serum protein ratio, body fluids:serum lactate dehydrogenase ratio, and serum lactate dehydrogenase

**Interpretation:** Elevated body fluid bilirubin is suggestive of an exudative fluid. This testing should be performed in conjunction with other testing including serum bilirubin analysis, body fluid:serum protein ratio, body fluids:serum lactate dehydrogenase ratio, and serum lactate dehydrogenase.

**Reference Values:**
Not applicable
The reference range has not been established for bilirubin in body fluids. The test result should be integrated into the clinical context for interpretation.

**Clinical References:**
4. Burgess LJ: Biochemical analysis of pleural, peritoneal and
Bili3
8452

Bilirubin, Serum

Clinical Information: Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect one or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes Type I and Type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In Type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is <20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:
DIRECT
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are <12 months of age.

TOTAL
<1 month: not established
1 month-17 years: < or =1.0 mg/dL
> or =18 years: < or =1.2 mg/dL

Bilirubin, Total, Serum

Clinical Information: Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from the red blood cell precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is a frequent and direct result of these disturbances. Jaundice can occur as a result of problems at each step in the metabolistic pathway. Disorders may be classified as those due to: increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The rare genetic disorders, Crigler-Najjar syndromes Type I and Type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In Type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown, While central nervous system damage is rare when total serum bilirubin (TSB) is <20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:
<1 month: not established
1 month-17 years: < or =1.0 mg/dL
> or =18 years: < or =1.2 mg/dL


Bilirubin, Urine

Clinical Information: Bilirubin is primarily derived from metabolism of hemoglobin. Only conjugated bilirubin is excreted into the urine and normally only trace amounts can be detected in urine. Elevated urinary bilirubin occurs in patients with obstructive jaundice or jaundice due to hepatocellular disease or injury. However, urine bilirubin is relatively insensitive for detection of liver disease.
Hyperbilirubinemia due to hemolysis is principally due to unconjugated bilirubin, and therefore does not result in increased urinary bilirubin.

**Useful For:** Limited use in screening of patients for liver disease.

**Interpretation:** Elevated urinary bilirubin is suggestive of hepatocellular disease or post-hepatic biliary obstruction.

**Reference Values:**
Negative
If positive, results reported as trace or positive.


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**BTDZ 35375**

**Biotinidase Deficiency, BTD Full Gene Analysis**

**Clinical Information:** Biotinidase deficiency is an inherited metabolic disease caused by reduced levels of biotinidase, an enzyme that recycles biotin by releasing it from its metabolic product, biocytin, or exogenous dietary proteins. Biotin is a vitamin that serves as a coenzyme for 4 carboxylases that are essential for amino acid catabolism, gluconeogenesis, and fatty acid synthesis. Depletion of free biotin reduces carboxylase activity, resulting in secondary carboxylase deficiency. Depending on the amount of residual biotinidase activity, individuals can have either profound or partial biotinidase deficiency. Age of onset and clinical phenotype vary among individuals. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. Untreated profound biotinidase deficiency (<10% of normal biotinidase activity) manifests within the first decade of life as seizures, hypotonia, neurosensory hearing loss, respiratory problems, and cutaneous symptoms including skin rash, alopecia, and recurrent viral or fungal infections. Among children and adolescents with profound biotinidase deficiency, clinical features include ataxia, sensorineural hearing loss, developmental delay, and eye problems such as optic neuropathy leading to blindness. Partial biotinidase deficiency (10%-30% of normal biotinidase activity) is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement. Treatment with biotin has been successful in both preventing and reversing the clinical features associated with biotinidase deficiency. As a result, biotinidase deficiency is included in most newborn screening programs in order to prevent disease. Biotinidase deficiency exhibits a similar clinical presentation to carboxylase and holocarboxylase synthetase deficiency. Therefore, measurement of the biotinidase enzyme is required to differentiate between these diseases and ensure proper diagnosis. Newborn screening for biotinidase deficiency involves direct analysis of the biotinidase enzyme from blood spots obtained shortly after birth. This enables early identification of potentially affected individuals and quick follow-up with confirmatory biochemical and molecular testing. Biotinidase deficiency is inherited in an autosomal recessive manner, caused by mutations in the biotinidase gene (BTD). The carrier frequency for biotinidase deficiency in the general population is about 1:120. Several common mutations in the BTD gene have been identified, accounting for about 60% of affected individuals. Sequencing of the entire BTD gene detects other, less common, disease-causing mutations. While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency. The recommended first-tier test to screen for biotinidase deficiency is a biochemical test that measures biotinidase enzyme activity, either newborn screening or BIOTS / Biotinidase, Serum. Molecular tests form the basis of confirmatory or carrier testing. Individuals with decreased enzyme activity are more likely to have 2 identifiable mutations in the BTD gene by molecular genetic testing.

**Useful For:** Second-tier test for confirming biotinidase deficiency (indicated by biochemical testing or newborn screening) Carrier testing of individuals with a family history of biotinidase deficiency, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

BIOTS
88205

Biotinidase, Serum

Clinical Information: Biotinidase deficiency is an autosomal recessive disorder caused by mutations in the biotinidase gene (BTD). Age of onset and clinical phenotype vary among individuals depending on the amount of residual biotinidase activity. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. The carrier frequency for biotinidase deficiency within the general population is about 1 in 120. Untreated profound biotinidase deficiency typically manifests within the first decade of life as seizures, ataxia, developmental delay, hypotonia, sensorineural hearing loss, vision problems, skin rash, and/or alopecia. Partial biotinidase deficiency is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement. Certain organic acidurias, such as holocarboxylase synthase deficiency, isolated carboxylase synthase deficiency and 3-methylcrotonylglycinuria, present similarly to biotinidase deficiency. Serum biotinidase levels can help rule out these disorders. Treatment with biotin is successful in preventing the clinical features associated with biotinidase deficiency. In symptomatic patients, treatment will reverse many of the clinical features except developmental delay and vision and hearing complications. As a result, biotinidase deficiency is included in most newborn screening programs. This enables early identification and treatment of presymptomatic patients. Molecular tests form the basis of confirmatory or carrier testing. When biotinidase enzyme activity is deficient, sequencing of the entire BTD gene (BTDZ / Biotinidase Deficiency, BTD Full Gene Analysis) allows for detection of disease-causing mutations in affected patients. Identification of familial mutations allows for testing of at-risk family members (FMTT / Familial Mutation, Targeted Testing). While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency.

Useful For: Preferred test for diagnosing biotinidase deficiency Follow-up testing for certain organic acidurias

Interpretation: The reference range is 3.5 U/L to 13.8 U/L. Partial deficiencies and carriers may occur at the low end of the reference range. Values <3.5 U/L are occasionally seen in specimens from unaffected patients.

Reference Values:
3.5-13.8 U/L

Clinical References:
Bird Fancier's Precipitin Panel I

Reference Values:

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<td>Canary Droppings</td>
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<tr>
<td>Chicken Serum</td>
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<tr>
<td>Pigeon/Dove Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Pigeon/Dove Serum</td>
<td>Negative</td>
</tr>
</tbody>
</table>

The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

Birt-Hogg-Dube Syndrome, Full Gene Analysis

Clinical Information: The clinical characteristics of Birt-Hogg-Dube syndrome (BHDS) include cutaneous manifestations (fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons), pulmonary cysts/history of pneumothorax, and various types of renal tumors. Skin lesions typically appear during the third and fourth decades of life and typically increase in size and number with age. Lung cysts are mostly bilateral and multifocal; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax. Individuals with BHDS have an increased risk of renal tumors that are typically bilateral and multifocal and usually slow growing; median age of tumor diagnosis is 48 years with a range from 31 to 71 years. Some families have renal tumor and/or autosomal dominant spontaneous pneumothorax without cutaneous manifestations. BHDS is inherited in an autosomal dominant manner and penetrance is considered to be very high. FLCN (also known as folliculin or BHD) is the only gene known to be associated with BHDS. Sequence analysis detects mutations in FLCN in 88% of affected individuals. Recent studies have reported that multi-exonic deletions can account for up to 5% to 10% of additional mutations.(2, 3) Molecular genetic testing is indicated in all individuals known to have or suspected of having BHDS, including individuals with one of the following: - Five or more facial or truncal papules with at least 1 histologically confirmed fibrofolliculoma, with or without a family history of BHDS - Facial papules histologically confirmed to be angiofibroma in an individual who does not fit the clinical criteria of tuberous sclerosis complex (TSC) or multiple endocrine neoplasia type 1 (MEN1) - Multiple and bilateral chromophobe, oncocytic, and/or hybrid renal tumors - A single oncocytic, chromophobe, or oncocytic hybrid renal tumor and a family history of renal cancer with any of these renal cell tumor family history of renal cancer with any of the above renal cell tumor types - A family history of autosomal dominant primary spontaneous pneumothorax without a history of smoking or chronic obstructive pulmonary disease (COPD) In the absence of an increased risk of developing childhood malignancy, the American Society of Clinical Oncology (ASCO) recommends delaying genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing.

Useful For: Genetic diagnosis of Birt-Hogg-Dube syndrome for clinical management, risk assessment for related clinical symptoms, and genetic counseling for family members.
**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FBISB 91143**
**Bismuth, Blood**
**Reference Values:**
Normal (Unexposed Population):
<50.0 ng/mL
Exposed: 100.0 ng/mL
Toxic: 200.0 ng/mL

**FBIS 91125**
**Bismuth, Serum**
**Reference Values:**
Reference Range: <4.0 ng/mL
Whole blood is the preferred specimen for assessment of Bismuth exposure.

**FBISU 91142**
**Bismuth, Urine**
**Reference Values:**
Units: ng/mL
Whole blood is the preferred specimen for assessment of Bismuth exposure.

**LCBK 89982**
**BK Virus, Molecular Detection, PCR, Plasma**
**Clinical Information:** Polyomaviruses are small (45 nm, approximately 5,000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance, Simian virus 40 (SV-40), JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected about 40 weeks (range 6-150) post-transplantation.(3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of
plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy. (4-8) Viral loads of > 10,000 copies/mL in plasma may indicate a risk for BKVAN (see QBKU / BK Virus, Molecular Detection, Quantitative, PCR, Plasma).

**Useful For:** Rapid detection of BK virus DNA

**Interpretation:** Results of plasma tests are reported in terms of the presence or absence of BK virus (BKV). Detection of BKV DNA in clinical specimens may support the clinical diagnosis of renal or urologic disease due to BKV. Correlation of qualitative results with clinical presentation and BK viral load in urine and/or plasma is recommended.

**Reference Values:**

**Negative**


**BK Virus, Molecular Detection, PCR, Urine**

**Clinical Information:** Polyomaviruses are small (45 nm, approximately 5,000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance; SV-40, JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans. (1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by age 5 and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected about 40 weeks (range 6-150) posttransplantation. (3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy. (4-8) However, BKV DNA is typically detectable in urine prior to plasma and may serve as an indication of impending BKVAN. Viral loads of > 100,000 copies/mL in urine may also indicate a risk for BKVAN (see QBKU / BK Virus, Molecular Detection, Quantitative, PCR, Urine).

**Useful For:** Rapid detection of BK virus DNA

**Interpretation:** Results of urine tests are reported in terms of the presence or absence of BK virus (BKV). Detection of BKV DNA in clinical specimens may support the clinical diagnosis of renal or urologic disease due to BKV. Correlation of qualitative results with clinical presentation and BK-viral load in urine and/or plasma is recommended.

**Reference Values:**

**Negative**


**BK Virus, Molecular Detection, Quantitative, PCR, Plasma**

**Clinical Information:** Polyomaviruses are small (45 nm, approximately 5,000 bp), DNA-containing viruses and include 3 closely related viruses of clinical significance: Simian virus 40 (SV-40), JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and BKV-associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected at about 40 weeks (range 6-150) posttransplantation.(3) Quantitative PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) The presence of BKV DNA in plasma at levels > or =10,000 copies BKV DNA/mL may correlate with an increased risk of BKVAN with this assay. Furthermore, the trend of viral DNA quantitation (eg, increasing, decreasing) may be helpful in predicting the onset of BKVAN.

**Useful For:** A prospective and diagnostic marker for the development of nephropathy in renal transplant recipients

**Interpretation:** Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads >10,000 copies/mL in plasma may also indicate a risk for BKVAN. This assay does not cross react with other polyomaviruses, including JC virus and Simian virus 40 (SV-40).

**Reference Values:** None detected


**BK Virus, Molecular Detection, Quantitative, PCR, Urine**

**Clinical Information:** Polyomaviruses are small (45 nm, approximately 5,000 bp), DNA-containing viruses and include 3 closely related viruses of clinical significance: SV-40, JC virus (JCV) and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and BKV-associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected at about 40 weeks (range 6-150) posttransplantation.(3) Quantitative PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) The presence of BKV DNA in plasma at levels > or =10,000 copies BKV DNA/mL may correlate with an increased risk of BKVAN with this assay. Furthermore, the trend of viral DNA quantitation (eg, increasing, decreasing) may be helpful in predicting the onset of BKVAN.

**Useful For:** A prospective and diagnostic marker for the development of nephropathy in renal transplant recipients

**Interpretation:** Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads >10,000 copies/mL in plasma may also indicate a risk for BKVAN. This assay does not cross react with other polyomaviruses, including JC virus and Simian virus 40 (SV-40).

**Reference Values:** None detected

productive infection only in humans.(1-2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected about 40 weeks (range 6-150) post-transplantation.(3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) However, BKV DNA is typically detectable in urine prior to plasma and may serve as an indication of impending BKVAN. Viral loads of >100,000 copies/mL in urine may also indicate a risk for BKVAN.

**Useful For:** A prospective and diagnostic marker for the development of BK virus nephropathy in renal transplant recipients

**Interpretation:** Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads of >100,000 copies/mL in urine may also indicate a risk for BKVAN. This assay does not cross react with other polyomaviruses, including JC virus and SV-40.

**Reference Values:**
None detected

**Clinical References:**
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>6</td>
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Reference values apply to all ages.


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**Blackberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Blastomyces Antibody by EIA, Serum**

**Clinical Information:** The dimorphic fungus, *Blastomyces dermatitidis*, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon.

**Useful For:** Detection of antibodies in patients having blastomycosis

**Interpretation:** A positive result indicates that IgG and/or IgM antibodies to Blastomyces were detected. The presence of antibodies is presumptive evidence that the patient was or is currently infected with (or exposed to) Blastomyces. A negative result indicates that antibodies to Blastomyces were not detected. The absence of antibodies is presumptive evidence that the patient was not infected with Blastomyces. However, the specimen may have been obtained before antibodies were detectable or the patient may be immunosuppressed. If infection is suspected, another specimen should be drawn 7 to 14 days later and submitted for testing. All specimens testing equivocal will be repeated. Specimens testing equivocal after repeat testing should be submitted for further testing by another conventional serologic test (eg, SBL / Blastomyces Antibody by Immunodiffusion, Serum).

**Reference Values:**
Negative


**CBLAS**

**Blastomyces Antibody by EIA, Spinal Fluid**

**Clinical Information:** The dimorphic fungus, *Blastomyces dermatitidis*, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

**Useful For:** Detection of antibodies in patients having blastomycosis

**Interpretation:** A positive result indicates that IgG and/or IgM antibodies to Blastomyces were detected. The presence of antibodies is presumptive evidence that the patient was or is currently infected with (or exposed to) Blastomyces. A negative result indicates that antibodies to Blastomyces were not detected, but does not rule out infection. All specimens testing equivocal will be repeated. Specimens testing equivocal after repeat testing should be submitted for further testing by another conventional serologic test (eg, CBL / Blastomyces Antibody by Immunodiffusion, Spinal Fluid).

**Reference Values:**
Negative

**Clinical References:** Kaufman L, Kovacs JA, Reiss E: Clinical immunomycology. In Manual of
Blastomyces Antibody by Immunodiffusion, Serum

Clinical Information: The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease - cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon.

Useful For: Detection of antibodies in patients having blastomycosis

Interpretation: A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Routine culture of clinical specimens (eg, respiratory specimen) is recommended in cases of suspected, active blastomycosis.

Reference Values:
Negative


Blastomyces Antibody by Immunodiffusion, Spinal Fluid

Clinical Information: The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease - cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

Useful For: Detection of antibodies in patients having blastomycosis

Interpretation: A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production, or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

Reference Values:
Negative


Bleeding Diathesis Profile, Limited

Clinical Information: Bleeding problems may be associated with a wide variety of coagulation abnormalities or may be due to problems not associated with coagulation (trauma and surgery as obvious examples). A partial listing of causes follows. -Deficiency or functional abnormality (congenital or acquired) of any of the following coagulation proteins: fibrinogen (factor I), factor II (prothrombin), factor V, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia C; bleeding severity not always proportionate to factor level), factor XIII (fibrin-stabilizing factor), von Willebrand factor (VWF antigen and activity), and alpha-2 plasmin inhibitor and plasminogen activator inhibitor (PAI-I; severe deficiency in rare cases). Neither alpha-2 plasmin inhibitor nor PAI-I are included.
as a routine bleeding diathesis assay component, but either can be performed if indicated or requested.

-Deficiency (thrombocytopenia) or functional abnormality of platelets such as congenital (Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc) and acquired (myeloproliferative disorders, uremia, drugs, etc) disorders. Platelet function abnormalities cannot be studied on mailed-in specimens.

-Specific factor inhibitors (most commonly directed against factor VIII); factor inhibitors occur in 10% to 15% of the hemophilia population and are more commonly associated with severe deficiencies of factor VIII or IX (antigen <1%). The inhibitor appears in response to transfusion therapy with factor concentrates with no correlation of occurrence and amount of therapy. Factor VIII inhibitors may occur spontaneously in the postpartum patient, with certain malignancies, in association with autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), in the elderly, and for no apparent reason. -Other acquired causes of increased bleeding include paraproteinemia; other factor-specific inhibitors, including those against factor V, factor XI; or virtually any of the coagulation proteins. -Acute disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), which is a fairly common cause of bleeding. Bleeding can also occur in patients with chronic ICF.

**Useful For:** Detection of the more common potential causes of abnormal bleeding (eg, factor deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors) and a simple screen to evaluate for an inhibitor or severe deficiency of factor XIII (rare).

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

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**BTROP 82374**

**Blomia tropicalis, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Blood Urea Nitrogen (BUN), Serum

Clinical Information: Urea is the final degradation product of protein and amino acid metabolism. In protein catabolism the proteins are broken down to amino acids and deaminated. The ammonia formed in this process is synthesized to urea in the liver. This is the most important catabolic pathway for eliminating excess nitrogen in the human body. Increased blood urea nitrogen (BUN) may be due to prerenal causes (cardiac decompensation, water depletion due to decreased intake and excessive loss, increased protein catabolism, and high protein diet), renal causes (acute glomerulonephritis, chronic nephritis, polycystic kidney disease, nephrosclerosis, and tubular necrosis) and postrenal causes (eg, all types of obstruction of the urinary tract, such as stones, enlarged prostate gland, tumors).

Useful For: The determination of serum blood urea nitrogen currently is the most widely used screening test for the evaluation of kidney function. The test is frequently requested along with the serum creatinine test since simultaneous determination of these 2 compounds appears to aid in the differential diagnosis of prerenal, renal and postrenal hyperuremia.

Interpretation: Serum blood urea nitrogen (BUN) determinations are considerably less sensitive than BUN clearance (and creatinine clearance) tests, and levels may not be abnormal until the BUN clearance has diminished to <50%. Clinicians frequently calculate a convenient relationship, the urea nitrogen/creatinine ratio: serum bun in mg/dL/serum creatinine in mg/dL. For a normal individual on a normal diet, the reference interval for the ratio ranges between 12 and 20, with most individuals being between 12 and 16. Significantly lower ratios denote acute tubular necrosis, low protein intake, starvation or severe liver disease. High ratios with normal creatinine levels may be noted with catabolic states of tissue breakdown, prerenal azotemia, high protein intake, etc. High ratios associated with high creatinine concentrations may denote either postrenal obstruction or prerenal azotemia superimposed on renal disease. Because of the variability of both the BUN and creatinine assays, the ratio is only a rough guide to the nature of the underlying abnormality. Its magnitude is not tightly regulated in health or disease and should not be considered an exact quantity.

Reference Values:
Males
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL
Reference values have not been established for patients who are <12 months of age.

Females
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL
Reference values have not been established for patients who are <12 months of age.

**Useful For:** Not established

**Interpretation:** None available

**Reference Values:**
Not applicable


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**Blood Worm, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>

**Clinical Information:** Bloom syndrome is characterized by short stature, sun sensitivity, susceptibility to infections, and a predisposition to cancer. Mutations in the BLM gene lead to genetic instability (increased chromosomal breakage and sister chromatid exchange) and cause the clinical manifestations of the syndrome. The protein encoded by the BLM gene is a helicase involved in maintaining DNA integrity. The carrier rate in the Ashkenazi Jewish population is 1 in 107. There is a common mutation in the Ashkenazi Jewish population: 2281delATCTGAins TAGATTC (2281del6/ins7). The carrier detection rate for this mutation is >99%.

**Useful For:** Carrier screening for Bloom syndrome in individuals of Ashkenazi Jewish ancestry Confirmation of suspected clinical diagnosis of Bloom syndrome in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis for Bloom syndrome in at-risk pregnancies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


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**Blue Mussel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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MUSS 82548

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Blueberry IgG**

**Interpretation:** mcg/mL of IgG

**Reference Values:**

- Lower Limit of Quantitation: 2.0
- Upper Limit of Quantitation: 200

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Blueberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**BMPRZ**

**Clinical Information:** Juvenile polyposis syndrome (JPS) is a rare hereditary cancer predisposition syndrome caused by mutations in the SMAD4 or BMPR1A genes. JPS is characterized by the presence of multiple histologically defined juvenile polyps in the upper and/or lower gastrointestinal (GI) tract and an increased risk for GI cancers. Age of onset for cancer development is typically in the second or third decade of life, although some patients present with a more severe infantile-onset form of the disease. JPS is inherited in an autosomal dominant fashion, although a significant proportion of probands have no family history. Approximately 50% of patients with JPS have an identifiable mutation in the SMAD4 or BMPR1A genes.

**Useful For:** Confirmation of juvenile polyposis syndrome for patients with clinical features This test should be ordered only for individuals with symptoms suggestive of juvenile polyposis syndrome. Asymptomatic patients with a family history of juvenile polyposis syndrome should not be tested until a mutation has been identified in an affected family member.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BMPR1A Gene, Full Gene Analysis**

**Clinical Information:** Bone alkaline phosphatase (BAP) is the bone-specific isoform of alkaline phosphatase. A glycoprotein that is found on the surface of osteoblasts, BAP reflects the biosynthetic activity of these bone-forming cells. BAP has been shown to be a sensitive and reliable indicator of bone metabolism. Normal bone is constantly undergoing remodeling in which bone degradation or resorption is balanced by bone formation. This process is necessary for maintaining bone health. If the process becomes uncoupled and the rate of resorption exceeds the rate of formation, the resulting bone loss can lead to osteoporosis and, consequently, a higher susceptibility to fractures. Osteoporosis is a metabolic bone disease characterized by low bone mass and abnormal bone microarchitecture. It can result from a number of clinical conditions including states of high bone turnover, endocrine disorders (primary and secondary hyperparathyroidism and thyrotoxicosis), osteomalacia, renal failure, gastrointestinal diseases, long-term corticosteroid therapy, multiple myeloma, and cancer metastatic to the bones. Paget disease is another common metabolic bone disease caused by excessive rates of bone metabolism.
remodeling resulting in local lesions of abnormal bone matrix. These lesions can result in fractures or neurological involvement. Antiresorptive therapies are used to restore the normal bone structure.

**Useful For:** Diagnosis and assessment of severity of metabolic bone disease including Paget disease, osteomalacia, and other states of high bone turnover Monitoring efficacy of antiresorptive therapies including postmenopausal osteoporosis treatment

**Interpretation:** Bone alkaline phosphatase (BAP) concentration is high in Paget disease and osteomalacia. Antiresorptive therapies lower BAP from baseline measurements in Paget disease, osteomalacia, and osteoporosis. Several studies have shown that antiresorptive therapies for management of osteoporosis patients should result in at least a 25% decrease in BAP within 3 to 6 months of initiating therapy. BAP also decreases following antiresorptive therapy in Paget disease. When used as a marker for monitoring purposes, it is important to determine the critical difference (or least significant change). The critical difference is defined as the difference between 2 determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level.

**Reference Values:**

**Males**

- <2 years: 25-221 mcg/L
- 2-9 years: 27-148 mcg/L
- 10-13 years: 35-169 mcg/L
- 14-17 years: 13-111 mcg/L
- Adults: < or =20 mcg/L

**Females**

- <2 years: 28-187 mcg/L
- 2-9 years: 31-152 mcg/L
- 10-13 years: 29-177 mcg/L
- 14-17 years: 7-41 mcg/L
- Adults
  - Premenopausal: < or =14 mcg/L
  - Postmenopausal: < or =22 mcg/L


**Bone Histomorphometry, Consultant Interpretation Only**

**Clinical Information:** Bone histomorphometry is a very sophisticated procedure utilizing full thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases including renal osteodystrophy, osteomalacia, and osteoporosis. Other information obtainable relate to disorders such as aluminum toxicity and iron abnormalities.

**Useful For:** Undetermined metabolic bone disease Renal osteodystrophy Osteomalacia Osteoporosis Paget's disease Assessing effects of therapy Identification of some disorders of the hematopoietic system Aluminum toxicity Presence of iron in the bone

**Interpretation:** Clinical endocrinologists trained in histomorphometric techniques review and interpret the histological appearance. A pathologist interprets the bone marrow from a hematoxylin and eosin-stained slide. No histomorphometric values are given.

**Reference Values:**
The laboratory will provide an interpretive report. All results will be called to the physician designated on the Bone Histomorphometry: Patient Information.

**Clinical References:** Recker RR: Bone Histomorphometry: Techniques and Interpretation. Boca Raton, FL, CRC Press, 1983

**Bone Histomorphometry, Qualitative**

**Clinical Information:** Bone histomorphometry is a very sophisticated procedure utilizing full thickness bone biopsy. Techniques such as 2 time-interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases, including renal osteodystrophy, osteomalacia, and osteoporosis, and other disorders such as aluminum toxicity and iron abnormalities.

**Useful For:** Undetermined metabolic bone disease Diagnosis of renal osteodystrophy Diagnosis of osteomalacia Diagnosis of osteoporosis Diagnosis of Paget's disease Assessing effects of therapy Identification of some disorders of the hematopoietic system Diagnosis of aluminum toxicity Identifying the presence of iron in the bone

**Interpretation:** Computer-generated histomorphometric values are given. Normal histomorphometric values for iliac crest are provided (female only). An interpretive report is provided.

**Reference Values:**
All results will be called to the physician designated on the Bone Histomorphometry: Patient Information.

**Clinical References:** Recker RR: Bone Histomorphometry: Techniques and Interpretation. Boca Raton, FL, CRC Press, 1983

**Bone Histomorphometry, Quantitative**

**Clinical Information:** Bone histomorphometry is a very sophisticated procedure utilizing full thickness bone biopsy. Techniques such as 2 time-interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases, including renal osteodystrophy, osteomalacia, and osteoporosis, and other disorders such as aluminum toxicity and iron abnormalities.

**Useful For:** Undetermined metabolic bone disease Renal osteodystrophy Osteomalacia Osteoporosis Paget's disease Assessing effects of therapy Identification of some disorders of the hematopoietic system Aluminum toxicity Presence of iron in the bone

**Interpretation:** Computer-generated histomorphometric values are given. Normal histomorphometric values for iliac crest are provided (female only). An interpretive report is provided.

**Reference Values:**
The laboratory will provide a quantitative and an interpretive report. All results will be called to the physician designated on the Bone Histomorphometry: Patient Information.

**Clinical References:** Recker RR: Bone Histomorphometry: Techniques and Interpretation. Boca Raton, FL, CRC Press, 1983

**Bordetella pertussis and Bordetella parapertussis, Molecular Detection, PCR**

**Clinical Information:** Bordetella pertussis is the highly contagious etiological agent of pertussis or whooping cough. Bordetella parapertussis causes a similar, but generally less severe illness. Despite
vaccination efforts, Bordetella pertussis remains common in the United States, underscoring the need for effective diagnostic tests. In the United States, pertussis is most common in the late summer months. Pertussis vaccination does not prevent Bordetella parapertussis infection, which generally occurs in a younger age group than disease caused by Bordetella pertussis. Diagnosis of pertussis is based on having a high clinical index of suspicion for the infection, along with confirmation by laboratory testing. Laboratory testing methods include nucleic acid amplification tests (eg, PCR), serology, culture and direct fluorescent antibody testing. Culture and direct fluorescent antibody testing are limited by low sensitivity, rendering nucleic acid amplification tests and serology the tests of choice. The Centers for Disease Control and Prevention recommends PCR testing for patients suspected of having acute pertussis. Bordetella pertussis PCR detects roughly twice as many cases as culture. Bordetella pertussis DNA can be detected up to 4 weeks, or longer (up to 8 weeks in our experience), after symptom onset. However, over time, the amount of Bordetella pertussis and Bordetella parapertussis DNA will diminish, rendering the assay less sensitive. A serologic response to Bordetella pertussis is typically mounted by 2 weeks following infection and, therefore, detection of IgG-class antibodies to pertussis toxin (PT), which is only produced by Bordetella pertussis, can be a useful adjunct for diagnosis at later stages of illness at a time when the amount of Bordetella pertussis may be below the limit of detection of the PCR assay.

**Useful For:** Preferred diagnostic test for the detection of Bordetella pertussis or Bordetella parapertussis

**Interpretation:** A positive result indicates the presence of DNA from Bordetella pertussis or Bordetella parapertussis. In some cases, a patient may test positive for both Bordetella pertussis and Bordetella parapertussis. Cross-reactivity with Bordetella holmesii and Bordetella bronchiseptica may occur with the Bordetella pertussis assay (see Cautions). A negative result indicates the absence of detectable Bordetella pertussis and Bordetella parapertussis DNA in the specimen but does not negate the presence of organism or active or recent disease (known inhibition rate of <1%) and may occur due to inhibition of PCR, sequence variability underlying primers and/or probes, or the presence of Bordetella pertussis or Bordetella parapertussis in quantities less than the limit of detection of the assay. Additionally, patients presenting late after symptom onset may test negative; in such cases, testing for Bordetella pertussis antibody, IgG, in serum may be considered.

**Reference Values:**
Not applicable

**Clinical References:**

**Bordetella pertussis Antibodies, IgA and IgG by ELISA with Reflex to Immunoblot**

**Reference Values:**
B. pertussis Ab, IgG 0.0 â€“ 0.9 U/mL
B. pertussis Ab, IgA <= 1.1 U/mL

**Bordetella pertussis IgG Antibodies, MAID**

**Reference Values:**
Reference Ranges:
- PT IgG <45 IU/mL
- FHA IgG <90 IU/mL
Levels of antibodies recognizing pertussis toxin (PT) and filamentous hemagglutinin antigen (FHA) are...
typically increased following either vaccination or natural exposure to Bordetella pertussis. Increased levels of FHA IgG alone may represent crossreactive antibodies induced by infection with other Bordetella species, Mycoplasma pneumoniae, Chlamydia pneumoniae, or nonencapsulated Haemophilus influenzae.

**BOAC 9723**

**Boron, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

Normally: Less than 100 mcg/L

**BOT 82715**

**Botrytis cinerea, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>0</td>
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<td>Negative</td>
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<td>1</td>
<td>0.35-0.69</td>
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<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
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**BOV 82135**

**Bovine Serum Albumin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Reference values** apply to all ages.


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**BXMPL 82876**

**Box Elder/Maple, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**BBRAF 35893**

**BRAF Analysis (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**BRAFC 35372**

**BRAF Mutation Analysis (V600), Melanoma**

**Clinical Information:** Assessment for BRAF V600 mutations has clinical utility in that it is a predictor of response to antimitant BRAF therapy. BRAF is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success with increases both in progression-free and overall survival in patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components. Malignant melanoma, one of the most aggressive forms of skin cancer, has a high frequency of BRAF mutations. Approximately 44% to 70% of melanoma cases have a BRAF mutation, and of those, approximately 50% to 90% are the V600E mutation. Current data suggest that the efficacy of BRAF-targeted therapies in melanoma is confined to patients with tumors with activating BRAF mutations, such as V600E, which leads to increased activation of the kinase pathway. While this test was designed to evaluate for the V600E alteration, cross-reactivity with other alterations at the V600 codon have been described. At this time, this test is approved specifically for melanoma tumors. Please refer to BRAFT / BRAF Mutation Analysis (V600E), Tumor for BRAF testing in nonmelanoma tumors.
Useful For: Identification of melanoma tumors that may respond to BRAF-targeted therapies

Interpretation: An interpretative report will be provided.


BRAF Mutation Analysis (V600E), Tumor

Clinical Information: Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in 1 of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6 and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPCC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation has not been identified to date in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having HNPCC/Lynch syndrome, especially when testing is performed in conjunction with MSIHC / Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, which includes MSI and IHC studies. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Hereditary Nonpolyposis Colorectal Cancer Testing Algorithm in Special Instructions. Also, see Hereditary Colorectal Cancer: Hereditary Nonpolyposis Colon Cancer (November 2005, Communicate') in Publications. Assessment for the BRAF V600E mutation has alternative clinical utilities. BRAF is part of the epidermal growth factor receptor (EGFR) signaling cascade, which plays a role in cell proliferation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success (increased progression-free and overall survival) in treating patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components.

Useful For: An adjunct to MSIHC / Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, when colon tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing in cases where colon tumor demonstrates MSI-H and loss of MLH1 protein expression. Note: Mayo's preferred screening test (BRMLH / MLH1 Hypermethylation and BRAF
Mutation Analyses, Tumor) includes both MLH1 promoter hypermethylation and BRAF V600E testing. To identify colon tumors with a previously negative KRAS mutation analysis result that may respond to epidermal growth factor receptor-targeted therapies. To identify melanoma tumors that may respond to anti-BRAF targeted therapies. Note: This is a laboratory developed test and has not been FDA-approved for this purpose.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Brazil Nut, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
> or =100 Strongly positive Reference values apply to all ages.


**C2729**

**Broccoli Carcinoma-Associated Antigen (CA 27.29), Serum**

Clinical Information: Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens that are large-molecular-weight glycoproteins with O-linked oligosaccharide chains. Monoclonal antibodies directed against these antigens have been developed, and several immunoassays are available to quantitate the levels of tumor-associated mucinous antigens in serum. The antibodies recognize epitopes of a breast cancer-associated antigen encoded by the human mucin 1 (MUC-1) gene, which is known by several names including MAM6, milk mucin antigen, CA 27.29, and cancer antigen 15-3 (CA 15-3). While CA 27.29 is expressed at the apical surface of normal epithelial cells, it is present throughout malignant epithelial cells of the breast, lung, ovary, pancreas, and other sites. The cancer-associated form of the antigen is less extensively glycosylated than the normal form and more specific for tumor cells.

Useful For: FDA-approved cancer-associated antigen (CA 27.29) for serial testing in women with prior stage II or III breast cancer who are clinically free of disease. Predicting early recurrence of disease in women with treated carcinoma of the breast. As an indication that additional tests or procedures should be performed to confirm recurrence of breast cancer.

Interpretation: Increased levels of cancer-associated antigen (CA 27.29) (>38 U/mL) may indicate recurrent disease in a woman with treated breast carcinoma.

Reference Values:
Males
> or =18 years: < or =38.0 U/mL (use not defined)
Females
> or =18 years: < or =38.0 U/mL
Reference values have not been established for patients who are <18 years of age.

Serum markers are not specific for malignancy, and values may vary by method.


**FBRCG**

**Broccoli IgG**

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Broccoli, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td>6</td>
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</tr>
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Reference values apply to all ages.


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**Brome Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**BRUGM 89476 Brucella Antibody Screen, IgG and IgM, Serum**

**Clinical Information:** Worldwide, brucellosis remains a major disease in humans and domesticated animals. Brucella infects goats (Brucella melitensis), cattle (Brucella abortus), swine (Brucella suis), and dogs (Brucella canis). The disease has a limited geographic distribution. Few cases occur in the United States, with the bulk occurring in the Mediterranean region, Western Asia, and parts of Latin America and Africa. Three species of Brucella commonly cause disease in humans: Brucella melitensis, Brucella suis, and Brucella abortus. The acute disease often presents with fever, chills, and malaise; the chronic form also causes abscesses in bone, brain, spleen, liver, and kidney.

**Useful For:** Evaluating patients with suspected brucellosis

**Interpretation:** In the acute stage of the disease there is an initial production of IgM antibodies, followed closely by production of IgG antibodies. IgG-class antibodies may decline after treatment; however, high levels of circulating IgG-class antibodies may be found without any active disease. Chronic brucellosis shows a predominance of IgG-class antibodies with little or no detectable IgM. Rising levels of specific antibody in paired sera can be regarded as serological evidence of recent infection. The presence of specific IgM in a single specimen may also indicate a recent infection, although IgM-class antibodies may persist for months following acute disease. The Centers for Disease Control and Prevention (CDC) recommends that specimens testing positive for IgG or IgM by enzyme-linked immunosorbent assay (ELISA) be confirmed by a Brucella-specific agglutination method.(2) The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes 1) Isolation of Brucella species from a clinical specimen, 2) Four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens obtained >2 weeks apart and studied at the same laboratory, or 3) Demonstration by immunofluorescence of Brucella species in a clinical specimen. Positive results by ELISA that are not
confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 7 to 14 days. If results of ELISA are negative and a recent infection is suspected, a new specimen should be tested after 7 to 14 days.

**Reference Values:**

**IgG SCREEN**
- Negative (reported as positive, negative, or equivocal)

**IgM SCREEN**
- Negative (reported as positive, negative, or equivocal)

**Clinical References:**
2. Public health consequences of a false-positive laboratory test result for Brucella–Florida, Georgia, and Michigan, 2005, MMWR Morb Mortal Wkly Rep June 6;2008/57(22);603-605

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**BRUC 8077**

**Brucella Culture**

**Clinical Information:** Brucella are facultative intracellular gram negative staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, Brucella suis, Brucella melitensis, and occasionally Brucella canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from blood, fluid (including urine), or tissue specimens.

**Useful For:** Diagnosis of brucellosis

**Interpretation:** Isolation of a Brucella species indicates infection. Cultures of blood and/or bone marrow are positive in 70% to 90% of acute Brucella infections, but much less so in subacute or chronic infections. In these latter instances, culture yield is highest from the specific tissue involved, or serology may be necessary to establish diagnosis.

**Reference Values:**
- Negative (reported as positive or negative)

**Clinical References:**

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**BRUCB 87345**

**Brucella Culture, Blood**

**Clinical Information:** Brucella species are facultative intracellular gram negative-staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, Brucella suis, Brucella melitensis, and occasionally Brucella canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from blood, fluid (including urine), or tissue specimens.

**Useful For:** Diagnosis of brucellosis

**Interpretation:** Isolation of a Brucella species indicates infection. Cultures of blood and/or bone marrow are positive in 70% to 90% of acute Brucella infections, but much less so in subacute or chronic
infections. In these latter instances, culture yield is highest from the specific tissue involved, or serology may be necessary to establish diagnosis.

**Reference Values:**
Negative (reported as positive or negative)


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**Brucella Total Antibody Confirmation, Agglutination, Serum**

**Clinical Information:** Brucella are facultative intracellular, gram-negative staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, Brucella suis, Brucella melitensis, and occasionally Brucella canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from bone marrow, blood, fluid (including urine), or tissue specimens. In cases of suspected brucellosis, serology may assist in the diagnosis and play a supplementary role to routine culture. Antibodies to Brucella species may not become detectable until 1 to 2 weeks following the onset of symptoms, so serum specimens drawn during acute disease may be negative by serology in patients with brucellosis. If serology is performed, the Centers for Disease Control and Prevention (CDC) currently recommends that specimens testing positive or equivocal for IgG or IgM by a screening EIA be confirmed by a Brucella-specific agglutination method. (1)

**Useful For:** Evaluating patients with suspected brucellosis

**Interpretation:** The Centers for Disease Control and Prevention (CDC) recommends that specimens testing positive or equivocal for IgG or IgM by a screening EIA be confirmed by a Brucella-specific agglutination method. (1) Negative to a titer of > or =1:40 can be seen in the normal, healthy population. A titer of > or =1:80 is often considered clinically significant; however, a 4-fold or greater increase in titer between acute and convalescent phase sera is required to diagnose acute infection. The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes 1) Isolation of Brucella species from a clinical specimen, 2) Four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens drawn >2 weeks apart and studied at the same laboratory, or 3) Demonstration by immunofluorescence of Brucella species in a clinical specimen. Positive results by a screening EIA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 7 to 14 days.

**Reference Values:**
<1:80


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**Brugada Syndrome Multi-Gene Panel, Blood**

**Clinical Information:** Brugada syndrome (BrS) is a genetic cardiac disorder characterized by ST segment elevation in leads V1-V3 on electrocardiography (EKG) with a high risk for ventricular arrhythmias that can lead to sudden cardiac death. BrS is inherited in an autosomal dominant manner and is caused by pathogenic variants in genes that encode cardiac ion channels. The diagnosis of BrS is
established based on the characteristic EKG abnormality along with personal and family health history, and also requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances. BrS has also been called sudden unexplained nocturnal death syndrome (SUNS) due to the tendency for syncope and sudden cardiac death to occur at rest or during sleep. The most common presentation of BrS is a male in his 40s with a history of syncopal episodes and malignant arrhythmias. However, presentation may occur at any age including infancy, where BrS may present as SIDS (sudden infant death syndrome). Published studies indicate that BrS is responsible for 4% to 12% of unexpected sudden deaths and for up to 20% of all sudden death in individuals with a structurally normal heart. The prevalence of BrS in the general population is difficult to determine due to the challenges of diagnosing the condition. In Southeast Asia where SUNDS is endemic, the prevalence of BrS is estimated to be 1 in 2,000. Of note, men are 8 to 10 times more likely to express symptoms of BrS, but the disease affects females as well and both sexes are at risk for ventricular arrhythmia and sudden death. Approximately 25% to 30% of BrS is accounted for by pathogenic variants in the genes known to cause the disorder, with the majority of cases attributed to the SCN5A gene. Although the majority of pathogenic variants identified to date have been detected by sequence analysis, large deletions in the SCN5A, SCN3B, CACNA1C, and KCNE3 genes have been reported in BrS. Genetic testing for BrS is supported by multiple consensus statements to confirm the diagnosis and identify at-risk family members. This is particularly important because the majority of patients with BrS are asymptomatic, but asymptomatic individuals may still be at increased risk for cardiac events. Pre- and post-test genetic counseling is an important factor in the diagnosis and management of BrS and is supported by expert consensus statements.

**Useful For:** Providing a genetic evaluation for patients with a personal or family history suggestive of Brugada syndrome Establishing a diagnosis of a Brugada syndrome, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**BSPR 82480**

**Brussel Sprouts, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders
Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense mutations are overrepresented 4-fold compared to substitutions, which indicates that the latter may be tolerated without causing a phenotype. The type and location of the mutation in the gene clearly affects the severity of the clinical phenotype. Some mutations manifest within the first year or 2 of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood.(5) Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same mutation is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK mutation.(5)

Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate(6) and for XLA, if a male parent is affected with the disease. A flow cytometry test for intracellular Btk in monocytes using an anti-Btk monoclonal antibody was developed by Futatani et al, which was used to evaluate both XLA patients and carriers.(7) In this study, 41 unrelated XLA families were studied and deficient Btk protein expression was seen in 40 of these 41 patients, with complete Btk deficiency in 35 patients and partial Btk deficiency in 5 patients. One patient had a normal level of Btk protein expression. The 6 patients with partial or normal Btk expression had missense BTK mutations. Additionally, the flow cytometry assay detected carrier status in the mothers of 35 of the 41 patients (approximately 85%). In the 6 patients where the Btk expression was normal in the mothers of XLA patients, it was noted that all these patients were sporadic cases without previous family history of the disease.(7) It appears, therefore, that most BTK mutations result in deficient expression of Btk protein, which can be detected by flow cytometry in monocytes.(7,8) Also, the mosaic expression of Btk protein in the monocytes by flow cytometry is potentially useful in the diagnosis of female carriers.(8) The flow cytometry test therefore provides a convenient screening tool for the diagnosis of XLA with confirmation of the diagnosis by BTK genotyping.(7,8) In the rare patient with the clinical features of XLA but normal Btk protein expression, BTK genotyping must be performed to determine the presence of a mutation. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). As well, some BTK mutations can preserve small numbers of circulating B cells and, therefore, all the 3 criteria mentioned above need to be evaluated. Patients should be assessed for the presence of Btk protein by flow cytometry, although normal results by flow cytometry do not rule out the presence of a BTK mutation with aberrant protein function (despite normal protein expression). The diagnosis is established or confirmed only in those individuals who have a mutation identified in the BTK gene by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells. Appropriate clinical history is required with or without abnormal Btk protein results by flow cytometry. It was shown that there are XLA patients with mothers who have normal Btk protein expression by flow cytometry and normal BTK genotyping and that the mutation in the patient is a result of de novo mutations in the maternal germline. In the same study, it was shown that there can be female carriers who have normal Btk protein expression but are genetically heterozygous and they do not show abnormal protein expression due to extreme skewed inactivation of the mutant X-chromosome.(6) Also, the presence of 1 copy of the normal BTK gene and associated normal Btk protein can stabilize mutant protein abrogating the typical bimodal pattern of protein expression seen in female carriers. Therefore, female carrier status can only conclusively be determined by genetic testing, especially if the Btk protein flow test is normal. It is important to keep in mind that the mere presence of BTK gene mutations does not necessarily correlate with a diagnosis of XLA unless the appropriate clinical and immunological features are present.(9,10)

**Useful For:** Preferred test for confirming a diagnosis of X-linked agammaglobulinemia (XLA) in males with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and <1% peripheral B cells. In females, this is the most useful test for identifying carriers of XLA. By including protein and gene analysis, this test provides a comprehensive assessment and enables appropriate genotype-phenotype correlations.

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**

BTKSP: An interpretive report will be provided.
BTK: Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).


BTKMP 89740

Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry

Clinical Information: X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by mutations in the Bruton tyrosine kinase gene (BTK), which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood. Approximately 85% of male patients with defects in early B-cell development have XLA. Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key clinical diagnostic characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year of age. BTK, the only gene associated with XLA, maps to the X-chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA. BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Bruton tyrosine kinase (Btk) protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Mutations causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Missense mutations account for 40% of all mutations, while nonsense mutations account for 17%, deletions 20%, insertions 7%, and splice-site mutations 16%. Over 600 unique mutations in the BTK gene have been detected by full gene sequencing and are listed in BTKbase, a database for BTK mutations (http://bioinf.uta.fi/BTKbase). Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense mutations are overrepresented 4-fold compared to substitutions, which indicates that the latter may be tolerated without causing a phenotype. The type and location of the mutation in the gene clearly affects the severity of the clinical phenotype. Some mutations manifest within the first year or 2 of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood. Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same mutation is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK mutation. Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate.
and for XLA, if a male parent is affected with the disease. A flow cytometry test for intracellular Btk in monocytes using an anti-Btk monoclonal antibody was developed by Futatani et al, which was used to evaluate both XLA patients and carriers.(7) In this study, 41 unrelated XLA families were studied and deficient Btk protein expression was seen in 40 of these 41 patients, with complete Btk deficiency in 35 patients and partial Btk deficiency in 5 patients. One patient had a normal level of Btk protein expression. The 6 patients with partial or normal Btk expression had missense BTK mutations. Additionally, the flow cytometry assay detected carrier status in the mothers of 35 of the 41 patients (approximately 85%). In the 6 patients where the Btk expression was normal in the mothers of XLA patients, it was noted that all these patients were sporadic cases without previous family history of the disease.(7) It appears, therefore, that most BTK mutations result in deficient expression of Btk protein, which can be detected by flow cytometry in monocytes.(7,8) Also, the mosaic expression of Btk protein in the monocytes by flow cytometry is potentially useful in the diagnosis of female carriers.(8) The flow cytometry test therefore provides a convenient screening tool for the diagnosis of XLA with confirmation of the diagnosis by BTK genotyping.(7,8) In the rare patient with the clinical features of XLA but normal Btk protein expression, BTK genotyping must be performed to determine the presence of a mutation. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). As well, some BTK mutations can preserve small numbers of circulating B cells and, therefore, all the 3 criteria mentioned above need to be evaluated. Patients should be assessed for the presence of Btk protein by flow cytometry, although normal results by flow cytometry do not rule out the presence of a BTK mutation with aberrant protein function (despite normal protein expression). The diagnosis is established or confirmed only in those individuals who have a mutation identified in the BTK gene by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells. Appropriate clinical history is required with or without abnormal Btk protein results by flow cytometry. It was shown that there are XLA patients with mothers who have normal Btk protein expression by flow cytometry and normal BTK genotyping and that the mutation in the patient is a result of de novo mutations in the maternal germline. In the same study, it was shown that there can be female carriers who have normal Btk protein expression but are genetically heterozygous, and they do not show abnormal protein expression due to extreme skewed inactivation of the mutant X chromosome.(6) Also, the presence of 1 copy of the normal BTK gene and associated normal Btk protein can stabilize mutant protein abrogating the typical bimodal pattern of protein expression seen in female carriers. Therefore, female carrier status can only conclusively be determined by genetic testing, especially if the Btk protein flow test is normal. It is important to keep in mind that the mere presence of BTK gene mutations does not necessarily correlate with a diagnosis of XLA unless the appropriate clinical and immunological features are present.(9,10)

**Useful For:** Preferred test for confirming a diagnosis of X-linked agammaglobulinemia (XLA) in male family members of affected individuals with known BTK mutations Preferred test for determining carrier status of female relatives of male XLA patients with known BTK mutations By including protein and gene analysis, this test provides a comprehensive assessment and enables appropriate genotype-phenotype correlations.

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**

BTKKM: An interpretive report will be provided.

BTK: Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).

**Clinical References:**

BTKs 89307

Bruton Tyrosine Kinase (BTK) Genotype, Full Gene Sequence

Clinical Information: X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1/200,000 live births. XLA is caused by mutations in the Bruton tyrosine kinase gene (BTK), which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood. Approximately 85% of male patients with defects in early B-cell development have XLA. Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinusopulmonary infections are among the key diagnostic clinical characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year. BTK, the only gene associated with XLA, maps to the X chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA. BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Btk protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Mutations causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Missense mutations account for 40% of all mutations, while nonsense mutations account for 17%, deletions 20%, insertions 7%, and splice-site mutations 16%. Over 600 unique mutations in BTK have been detected by full gene sequencing and are listed in BTKbase, a database for BTK mutations (http://bioinf.uta.fi/BTKbase). Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense mutations are overrepresented 4-fold compared with substitutions, which indicates that the latter may be tolerated without causing a phenotype. The type and location of the mutation in the gene clearly affects the severity of the clinical phenotype. Some mutations manifest within the first 2 years of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or adulthood. Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same mutation is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK mutation. Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate and for XLA, if a male parent is affected with the disease. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). As well, some BTK mutations can preserve small numbers of circulating B cells and, therefore, all 3 of the criteria mentioned above need to be evaluated. The preferred approach for confirming a diagnosis of XLA in males and identifying carrier females requires testing for the Btk protein expression on B cells by flow cytometry and genetic testing for a BTK mutation. Patients can be screened for the presence of Btk protein by flow cytometry (BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood); however, normal results by flow cytometry do not rule out the presence of a BTK mutation with normal protein expression but aberrant protein function. The diagnosis is confirmed only in those individuals with appropriate clinical history who have a mutation identified within BTK by gene sequencing or who have male family
members with hypogammaglobulinemia with absent or low B cells.

**Useful For:** Confirming a diagnosis of X-linked agammaglobulinemia (XLA) in male patients with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and <1% peripheral B cells, with or without abnormal Bruton tyrosine kinase (Btk) protein expression by flow cytometry. Follow-up testing when evaluating symptomatic male family members with an abnormal or equivocal result for Btk-protein expression by flow cytometry (BTK/Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood) Evaluating for the presence of BTK mutations in female relatives (of male XLA patients) who do not demonstrate carrier phenotype by Btk flow cytometry. Because genotype-phenotype correlation is important for the diagnosis of XLA, the preferred test for confirming a diagnosis of XLA in males and identifying carrier females is BTKFP/Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry.

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BTKK 89306**

**Bruton Tyrosine Kinase (BTK) Genotype, Known Mutation**

**Clinical Information:** X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1/200,000 live births. XLA is caused by mutations in the Bruton tyrosine kinase gene (BTK),(1) which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood.(2) Approximately 85% of male patients with defects in early B-cell development have XLA.(3) Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key diagnostic clinical characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year. BTK, the only gene associated with XLA, maps to the X chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA.(4) BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Btk protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Mutations causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Missense mutations account for 40% of all mutations, while nonsense mutations account for 17%, deletions 20%, insertions 7%, and splice-site mutations 16%. Over 600 unique mutations in BTK have been detected by full gene sequencing and are listed in the BTKbase, a database for BTK mutations (http://bioinf.uta.fi/BTKbase).(5) Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense mutations are overrepresented 4-fold compared with substitutions, which indicates that the latter may be tolerated without causing a phenotype. The type and location of the mutation in the gene clearly affects the severity of the clinical phenotype. Some mutations manifest within the first 2 years of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood.(5) Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same mutation is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably...
depending on the nature of the specific BTK mutation.(5) Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate(6) and for XLA, if a male parent is affected with the disease. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). As well, some BTK mutations can preserve small numbers of circulating B cells and, therefore, all 3 of the criteria mentioned above need to be evaluated. The preferred approach for confirming a diagnosis of XLA in males and identifying carrier females requires testing for the Btk protein expression on B cells by flow cytometry and genetic testing for a BTK mutation. Patients can be screened for the presence of Btk protein by flow cytometry (BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood); however, normal results by flow cytometry do not rule out the presence of a BTK mutation with normal protein expression but aberrant protein function. The diagnosis is confirmed only in those individuals with appropriate clinical history who have a mutation identified within BTK by gene sequencing or who have other male family members with hypogammaglobulinemia with absent or low B cells.

Useful For: As a follow-up confirmatory genetic test for relatives of X-linked agammaglobulinemia (XLA) patients with a previously identified Bruton tyrosine kinase gene (BTK) mutation, after abnormal Btk protein expression has been previously demonstrated (eg, BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood) Because genotype-phenotype correlations are important, the preferred test for confirming a diagnosis of XLA in males and identifying carrier females in families where a BTK mutation has already been identified is BTKMP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry, which provides a comprehensive assessment of both protein and DNA analysis.

Interpretation: A patient-specific interpretive report is provided.

Reference Values: An interpretive report will be provided.


**BTK**

**Bruton Tyrosine Kinase (Btk), Protein Expression, Flow Cytometry, Blood**

**Clinical Information:** The differential diagnosis for patients with primary hypogammaglobulinemia of unclear etiology (after other secondary causes of hypogammaglobulinemia have been ruled out) includes common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA). CVID is the most common diagnosis of humoral immunodeficiency, particularly in adults, but also in children over 4 years of age. However, adult male patients with XLA may be misdiagnosed with CVID. XLA is an independent humoral immunodeficiency and should not be regarded as a subset of CVID. The BTK gene is present on the long arm of the X-chromosome and encodes for a cytoplasmic tyrosine kinase with 5 distinct structural domains. While BTK gene sequencing is the gold standard for definitively identifying mutations and confirming a diagnosis of XLA, it is labor intensive and expensive. Flow cytometry is a
screening test for XLA and should be included in the evaluation of patients with possible CVID, particularly in male patients with <1% B cells. Bruton tyrosine kinase (Btk) is an intracellular protein and absence of the Btk protein by flow cytometry provides a strong rationale for performing a BTK gene-sequencing test. However, 20% to 30% of XLA patients may have intact or truncated Btk protein with abnormal function; therefore, genetic analysis remains the more definitive test for diagnosing XLA (besides other clinical and immunological parameters). XLA is a prototypical humoral immunodeficiency caused by mutations in the BTK gene, which encodes Btk, a hematopoietic-specific tyrosine kinase. XLA is characterized by normal, reduced, or absent Btk expression in monocytes and platelets, a significant reduction or absence of circulating B cells in blood, and profound hypogammaglobulinemia of all isotypes (IgG, IgA, IgM, and IgE). The clinical presentation includes early onset of recurrent bacterial infections, and absent lymph nodes and tonsils. Btk plays a critical role in B-cell differentiation. The defect in Btk may be "leaky" in some patients (ie, a consequence of mutations in the gene that result in a milder clinical and laboratory phenotype), such that these patients may have some levels of IgG and/or IgM and a small number of B cells in blood.(1) The vast majority of XLA patients are diagnosed in childhood (median age of diagnosis in patients with sporadic XLA is 26 months), although some patients are recognized in early adulthood or later in life. The diagnosis of XLA in both children and adults indicates that the disorder demonstrates considerable clinical phenotypic heterogeneity, depending on the position of the mutations within the gene. Females are typically carriers and asymptomatic. Testing in adult females should be limited to those in their child-bearing years (<45 years). Carrier testing ideally should be confirmed by genetic testing since it is possible to have a normal flow cytometry test for protein expression in the presence of heterozygous (carrier) BTK gene mutations. Flow cytometry is a preliminary screening test for XLA. It is important to keep in mind that this flow cytometry test is only a screening tool and approximately 20% to 30% of patients who have a mutation within the BTK gene have normal protein expression (again related to the position of the mutation in the gene and the antibody used for flow cytometric analysis). Therefore, in addition to clinical correlation, genetic testing is recommended to confirm a diagnosis of XLA. Furthermore, it is helpful to correlate gene and protein data with clinical history (genotype-phenotype correlation) in making a final diagnosis of XLA. Consequently, the preferred test for XLA is BTKFP / Bruton's Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry, which includes both flow cytometry and gene sequencing to confirm the presence of a BTK mutation. If a familial mutation has already been identified, then BTKMP / Bruton's Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry should be ordered.

**Useful For:** Preliminary screening for X-linked agammaglobulinemia (XLA), primarily in male patients (<65 years of age) or female carriers (child-bearing age: <45 years) Because genotype-phenotype correlations are important, the preferred test for confirming a diagnosis of XLA in males and identifying carrier females is: -BTKFP / Bruton's Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry -In families where a BTK mutation has already been identified, order BTKMP / Bruton's Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry.

**Interpretation:** Results are reported as Bruton tyrosine kinase (Btk) protein expression present (normal) or absent (abnormal) in monocytes. Additionally, mosaic Btk expression (indicative of a carrier) and reduced Btk expression (consistent with partial Btk protein deficiency) are reported when present and correlated with a healthy experimental control. BTK genotyping (BTKS / Bruton’s Tyrosine Kinase (BTK) Genotype, Full Gene Sequence or BTKK / Bruton's Tyrosine Kinase (BTK) Genotype, Known Mutation) should be performed in the following situations: -To confirm any abnormal flow cytometry result -In the rare patient with the clinical features of X-linked agammaglobulinemia (XLA), but normal Btk protein expression -In mothers of patients who do not show the classic carrier pattern of bimodal protein expression (to determine if there is maternal germinal mosaicism or skewed mutant X-chromosome inactivation) or there is dominant expression of the normal protein in the presence of 1 copy of a mutation

**Reference Values:**
Present

- Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).


**BUCW 82727**

**Buckwheat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<td>0.70-3.49</td>
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<tr>
<td>4</td>
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<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
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<td>Strongly positive Reference values apply to all ages.</td>
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**BDRP 82791**

**Budgerigar Droppings, IgE**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>&gt; or =100</td>
<td>Strongly positive</td>
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</table>

Reference values apply to all ages.


BFTH 82779

Budgerigar Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease...
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Bullous Pemphigoid, BP180 and BP230, IgG Antibodies, Serum**

**Clinical Information:** Bullous pemphigoid (BP) is chronic pruritic blistering disorder found mainly in aged persons, characterized by the development of tense blisters over an erythematous or urticarial base. IgG antibasement membrane zone antibodies are found in the serum of patients, and linear IgG and C3 sediment is found on the basement membrane zone of the lesion. Several well characterized variants exist including localized, mucous membrane predominant and pemphigoid gestationis, also referred to as herpes gestationis. Target antigens of the autoantibodies in BP patient serum are BP230 and BP180 also called BPAG1 and BPAG2. Molecular weight of these antigens is 230 kD and 180 kD, respectively. BP180 is thought to be the direct target of the autoantibody because of its location along the basement membranes, and the autoantibody against BP230 is thought to be secondarily produced.

**Useful For:** Bullous pemphigoid (BP) BP180 and BP230 enzyme-linked immunosorbent assay are sensitive, objective, and specific tests that should be considered as an initial screening test in the diagnosis of pemphigoid and its variants. To compare these results with the standard serum test of indirect immunofluorescence utilizing monkey esophagus substrate.

**Interpretation:** Antibodies to bullous pemphigoid (BP) BP180 and BP230 have been shown to be present in most patients with pemphigoid. Adequate sensitivities and specificity for disease are documented and Mayo’s experience demonstrates a very good correlation between BP180 and BP230 results and the presence of pemphigoid (see Supportive Data). However, in those patients strongly suspected to have pemphigoid, either by clinical findings or by routine biopsy, and in whom the BP180/BP230 assay is negative, follow-up testing by CIFS/ Cutaneous Immunofluorescence Antibodies (IgG), Serum is recommended. Antibody titer correlates with disease activity in many patients. Patients with severe disease can usually be expected to have high titers of antibodies to BP. Titers are expected to decrease with clinical improvement. For further information, see Cutaneous Immunofluorescence Testing in Special Instructions.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
BP180
<9.0 U (negative)
≥9.0 U (positive)

BP230
<9.0 U (negative)
≥9.0 U (positive)


**Bupivacaine, Serum**

**Clinical Information**: Bupivacaine (1-butyl-N-[2,6-dimethylphenyl] piperidine-2-carboxamide) is used as a local anesthetic for many surgical procedures, and is injected directly into surgical sites to reduce pain for up to 20 hours postsurgery. As an injectable local anesthetic, the drug is used to effect peripheral, sympathetic, caudal, epidural, or retrobulbar nerve membrane permeability to sodium ions, which results in inhibition of depolarization with resultant conduction blockade.(1) The onset and duration of anesthesia is route- and dose-dependent, ranging from 1 to 17 minutes and lasting for 2 to 9 hours.(1) The drug is highly protein bound (approximately 95%), and has a volume of distribution (Vd) of 0.4 L/kg to 1.0 L/kg. Bupivacaine under goes significant metabolism; <1% of a dose is excreted unchanged.(2) The half-life elimination is age-dependent: approximately 8 hours in neonates and 1.5 to 5.5 hours in adults.(1) Serum levels of bupivacaine correlate poorly with anesthesia effect because the drug's distribution out of the injection site is variable. However, serum levels may have value in indicating potential toxicity remote from the injection site. In general, central nervous system (CNS) and cardiovascular events are the primary toxicities and include tremor, tinnitus, dizziness, blurred vision, hypotension, and bradycardia. CNS symptoms of toxicity appear at lower serum levels than do cardiovascular symptoms.(3) Intralipid has been proposed as a treatment for the cardiotoxicity, but neither the optimum dose nor guidelines for intervention have been defined, so its use remains controversial and limited to those cases of cardiotoxicity when cardiopulmonary bypass is the only other option. The drug is now available as the principally active optical isomer, levobupivacaine (this assay measures levobupivacaine and the racemic mixture [levobupivacaine and bupivacaine] equally). The occurrence of CNS toxicity with use of levobupivacaine is 1.5 to 2.5 times lower than with bupivacaine, from studies in healthy volunteers, with CNS toxicity onset coming at approximately 25% higher doses.(4) Since both drugs are often administered for local anesthesia at levels near the top of the tolerated range, it has proven difficult to objectively assess potency, and there is no clear conclusion as to which drug is more potent.

**Useful For**: Assessment of possible central nervous system or cardiac toxicity associated with use of bupivacaine or levobupivacaine

**Interpretation**: In trials with healthy volunteers, the threshold for central nervous system (CNS) toxicity has been reported at 2.1 (+/- 1.2) mg/L following intravenous infusion,(3) and in another trial, 13 of 14 healthy volunteers reported signs of CNS toxicity at 2.25 mg/L of racemic bupivacaine.(5) Cardiovascular symptoms were reported in many fewer subjects, indicating slightly higher threshold for cardiovascular toxicity.

**Reference Values**: No established reference values

Buprenorphine and Norbuprenorphine, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin. Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent. As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one-fifth of the potency of its parent. The glucuronide metabolites are inactive. The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have strayed from opioid dependence therapy.

Useful For: Monitoring of compliance utilizing buprenorphine Detection and confirmation of the illicit use of buprenorphine

Interpretation: The presence of buprenorphine >0.5 ng/mL or norbuprenorphine >0.5 ng/mL is a strong indicator that the patient has used buprenorphine.

Reference Values:
Negative
Cutoff concentrations:
Buprenorphine: 0.5 ng/mL
Norbuprenorphine: 0.5 ng/mL


Buprenorphine Screen with Reflex, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial...
mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.\(^{(1)}\) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent.\(^{(1)}\) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive.\(^{(1)}\) This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can have a false-negative due to the antibody's ability to cross-react with different drugs in the target class.

**Useful For:** Screening for drug abuse or use of buprenorphine

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**

Negative
Screening cutoff concentration:
Buprenorphine: 5 ng/mL.


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**Buprenorphine Screen, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.\(^{(1)}\) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent.\(^{(1)}\) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive.\(^{(1)}\) This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can have a false-negative due to the antibody's ability to cross-react with different drugs in the target class.

**Useful For:** Screening for drug abuse or use of buprenorphine

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to
Reference Values:
Negative
Screening cutoff concentration:
Buprenorphine: 5 ng/mL


FBUHB 57395

Bupropion (Wellbutrin, Zyban) and Hydroxybupropion

Reference Values:
Bupropion: 50-100 ng/mL
Hydroxybupropion: 600-2000 ng/mL

Note: Expected concentration range for hydroxybupropion: 600 â€“ 2000 ng/mL.

FBUS 91115

Buspirone (Buspar)

Reference Values:
Units: ng/mL

Therapeutic and toxic ranges have not been established.

Expected serum buspirone concentrations in patients taking recommended daily dosages: up to 10.00 ng/mL.

BUAUC 83188

Busulfan, Intravenous Dose, Area Under the Curve (AUC), Plasma

Clinical Information: Busulfan is an alkylating agent used to ablate bone marrow cells prior to hematopoietic stem cell transplantation for chronic myelogenous leukemia. (1) Busulfan is typically administered intravenously (IV) at the recommended dosage of 0.8 mg/kg of actual or ideal body weight (whichever is lower) and given once every 6 hours over 4 days for a total of 16 doses. Dose-limiting toxicity of busulfan includes veno-occlusive liver disease, seizures, and coma. To avoid toxicity while ensuring busulfan dose adequacy to completely ablate the bone marrow, IV dosing should be guided by pharmacokinetic (PK) evaluation of area under the curve (AUC) and clearance after the first dose. (2) The PK evaluation should be carried out at the end of the first dose, with results of PK testing available to facilitate dose adjustment before beginning the fifth dose.

Useful For: Guiding dosage adjustments to achieve complete bone marrow ablation while minimizing dose-dependent toxicity

Interpretation: This test should only be ordered when the following criteria are met: -Busulfan dosing protocol must be intravenous (IV) administration of 8 mg/kg doses every 6 hours over 4 days, for a total of 16 doses -Specimens must be drawn as described below: - 1 specimen drawn immediately after termination of a 2-hour IV infusion of busulfan - 1 specimen drawn 1 hour after the infusion is terminated - 1 specimen drawn 2 hours after the infusion is terminated - 1 specimen drawn 4 hours after the infusion is terminated These results will be used to calculate a 6-hour area under the curve (AUC). If a different dosing or specimen collection protocol is used, or if different calculations are required, please contact the Laboratory Director. The optimal result for AUC (6 hour) derived from this pharmacokinetic (PK) evaluation of IV busulfan is 1,100 (mcmol/L)(min). AUC results >1,500 (mcmol/L)(min) are associated with hepatic veno-occlusive disease. A dose reduction should be considered before the next busulfan
infusion. AUC results <900 (mcmol/L)(min) are consistent with incomplete bone marrow ablation. A dose increase should be considered before the next busulfan infusion. Clearance of busulfan in patients with normal renal function is usually in the range of 2.1 to 3.5 (mL/min)/kg. Elevated AUC is typically associated with clearance <2.5 (mL/min)/kg, most frequently due to diminished activity of glutathione S-transferase A1-1 activity.(3)

Reference Values:
AREA UNDER THE CURVE
900-1,500 (mcmol/L)(min)
CLEARANCE
2.1-3.5 (mL/minute)/kg


BUTAS 8427

Butalbital, Serum

Clinical Information: Butalbital is a short-acting barbiturate with hypnotic properties that is used in combination with other drugs such as acetaminophen, salicylate, caffeine, and codeine.(1) Butalbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a volume of distribution (Vd) of 0.8 L/kg, and about 26% of a dose is bound to plasma proteins. Butalbital's half-life is about 35 to 88 hours. Excretion occurs mainly in the urine.(1,2)

Useful For: Monitoring butalbital therapy

Interpretation: Butalbital level > or =10 mcg/mL is toxic

Reference Values:
<10 mcg/mL


CPR 8804

C-Peptide, Serum

Clinical Information: C-peptide (connecting peptide), a 31-amino-acid polypeptide, represents the midportion of the proinsulin molecule. Proinsulin resembles a hairpin structure, with the N-terminal and C-terminal, which correspond to the A and B chains of the mature insulin molecule, oriented parallel to each other and linked by disulfide bonds. The looped portion of the hairpin between the A and B chains is called C-peptide. During insulin secretion it is enzymatically cleaved off and cosecreted in equimolar proportion with mature insulin molecules. Following secretion, insulin and C-peptide enter the portal circulation and are routed through the liver, where at least 50% of the insulin binds to receptors, initiates specific hepatic actions (stimulation of hepatic glucose uptake and suppression of glycogenolysis, gluconeogenesis, and ketogenesis) and is subsequently degraded. Most of the insulin molecules that pass through the liver into the main circulation bind to peripheral insulin receptors, promoting glucose uptake, while the remaining molecules undergo renal elimination. Unlike insulin, C-peptide is subject to neither hepatic nor significant peripheral degradation, but is mainly removed by the kidneys. As a result, C-peptide has a longer half-life than insulin (30-35 minutes versus 5-10 minutes) and the molar ratio of
circulating insulin to circulating C-peptide is generally <1, despite equimolar secretion. Until recently, C-peptide was thought to have no physiological function, but it now appears that there may be specific C-peptide cell-surface receptors (most likely belonging to the super-family of G-protein coupled receptors), which influence endothelial responsiveness and skeletal and renal blood flow. In most disease conditions associated with abnormal serum insulin levels, the changes in serum C-peptide levels parallel insulin-related alterations (insulin to C-peptide molar ratio < or =1). Both serum C-peptide and serum insulin levels are elevated in renal failure and in disease states that lead to augmented primary endogenous insulin secretion (eg, insulinoma, sulfonylurea intoxication). Both also may be raised in any disease states that cause secondary increases in endogenous insulin secretion mediated through insulin resistance, primarily obesity, glucose intolerance, and early type 2 diabetes mellitus (DM), as well as endocrine disorders associated with hypersecretion of insulin-antagonistic hormones (eg, Cushing syndrome, acromegaly). Failing insulin secretion in type 1 DM and longstanding type 2 DM is associated with corresponding reductions in serum C-peptide levels. Discordant serum insulin and serum C-peptide abnormalities are mainly observed in 2 situations: exogenous insulin administration and in the presence of anti-insulin autoantibodies. Factitious hypoglycemia due to surreptitious insulin administration results in appropriate suppression of endogenous insulin and C-peptide secretion. At the same time, the peripherally administered insulin bypasses the hepatic first-pass metabolism. In these situations, insulin levels are elevated and C-peptide levels are decreased. In patients with insulin antibodies, insulin levels are increased because of the prolonged half-life of autoantibody-bound insulin. Some patients with anti-idiotypic anti-insulin autoantibodies experience episodic hypoglycemia caused by displacement of autoantibody-bound insulin.

**Useful For:** Diagnostic workup of hypoglycemia: -Diagnosis of factitious hypoglycemia due to surreptitious administration of insulin -Evaluation of possible insulinoma -Surrogate measure for the absence or presence of physiological suppressibility of endogenous insulin secretion during diagnostic insulin-induced hypoglycemia (C-peptide suppression test) Assessing insulin secretory reserve in selected diabetic patients (as listed below) who either have insulin autoantibodies or who are receiving insulin therapy: -Assessing residual endogenous insulin secretory reserve -Monitoring pancreatic and islet cell transplant function -Monitoring immunomodulatory therapy aimed at slowing progression of preclinical, or very early stage type 1 diabetes mellitus

**Interpretation:** To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio):
-Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L
-Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L
Factitious hypoglycemia due to surreptitious insulin administration results in elevated serum insulin levels and low or undetectable C-peptide levels, with a clear reversal of the physiological molar insulin to C-peptide ratio (< or =1) to an insulin to C-peptide ratio of >1. By contrast, insulin and C-peptide levels are both elevated in insulinoma and the insulin to C-peptide molar ratio is < or =1. Sulfonylurea ingestion also is associated with preservation of the insulin to C-peptide molar ratio of < or =1. In patients with insulin autoantibodies, the insulin to C-peptide ratio may be reversed to >1, because of the prolonged half-life of autoantibody-bound insulin. Dynamic testing may be necessary in the workup of hypoglycemia; the C-peptide suppression test is most commonly employed. C-peptide levels are measured following induction of hypoglycemia through exogenous insulin administration. The test relies on the demonstration of the lack of suppression of serum C-peptide levels within 2 hours following insulin-induced hypoglycemia in patients with insulinoma. Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

**Reference Values:**
1.1-4.4 ng/mL
Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

**Clinical References:**
C-Reactive Protein (CRP), Serum

Clinical Information: C-reactive protein (CRP) is one of the most sensitive acute-phase reactants for inflammation. CRP is synthesized by the liver and consists of 5 identical polypeptide chains that form a 5-membered ring with a molecular weight of 105,000 daltons. Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever. CRP elevations are nonspecific and may be useful for the detection of systemic inflammatory processes; to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, eg, in patients suffering from systemic lupus erythematosus or colitis ulcerosa; to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy; to determine the presence of postoperative complications at an early stage, such as infected wounds, thrombosis, and pneumonia; and to distinguish between infection and bone marrow rejection. Postoperative monitoring of CRP levels of patients can aid in the recognition of unexpected complications (persisting high or increasing levels). Measuring changes in the concentration of CRP provides useful diagnostic information about the level of acuity and severity of a disease. It also allows judgments about the disease genesis. Persistence of a high serum CRP concentration is usually a grave prognostic sign that generally indicates the presence of an uncontrolled infection.

Useful For: Detecting systemic inflammatory processes Detecting infection and assessing response to antibiotic treatment of bacterial infections Differentiating between active and inactive disease forms with concurrent infection HSCRP / C-Reactive Protein, High Sensitivity, Serum is the appropriate C-reactive protein test to order to assess risk of cardiovascular disease or events

Interpretation: In normal healthy individuals, C-reactive protein (CRP) is a trace protein (<8 mg/L). Elevated values are consistent with an acute inflammatory process. After onset of an acute phase response, the serum CRP concentration rises rapidly (within 6-12 hours and peaks at 24-48 hours) and extensively. Concentrations above 100 mg/L are associated with severe stimuli such as major trauma and severe infection (sepsis).

Reference Values:
< or =8.0 mg/L


C-Reactive Protein, High Sensitivity, Serum

Clinical Information: C-reactive protein (CRP) is a biomarker of inflammation. Plasma CRP concentrations increase rapidly and dramatically (100-fold or more) in response to tissue injury or inflammation. High-sensitivity CRP (hs-CRP) is more precise than standard CRP when measuring baseline (ie, normal) concentrations and enables a measure of chronic inflammation. Atherosclerosis is an inflammatory disease and hs-CRP has been endorsed by multiple guidelines as a biomarker of atherosclerotic cardiovascular disease risk.(European 2011, Goff 2013, Jacobson 2014) A large prospective clinical trial demonstrated significantly less cardiovascular risk for patients with hs-CRP <2.0 mg/L.(1) More aggressive treatment strategies may be warranted in patients with hs-CRP ≥2.0mg/L.

Useful For: Assessment of risk of developing myocardial infarction in patients presenting with acute coronary syndromes Assessment of risk of developing cardiovascular disease or ischemic events in individuals who do not manifest disease at present

Interpretation: Values >2.0 mg/L suggest an increased likelihood of developing cardiovascular disease or ischemic events.

Reference Values:
Lower risk: <2.0 mg/L  
Higher risk: > or =2.0 mg/L  
Acute inflammation: >10.0 mg/L


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**C1ES 8198**

**C1 Esterase (C1ES) Inhibitor Antigen, Serum**

**Clinical Information:** C1 esterase inhibitor blocks the activation of C1 (first component of the complement cascade) to its active form. The deficiency of C1 esterase inhibitor results in the inappropriate activation of C1 and the subsequent release of an activation peptide from C2 with kinin-like activity. This kinin-like peptide enhances vascular permeability. C1 esterase inhibitor deficiency results in hereditary or acquired angioedema. This disease is an autosomal dominant inherited condition, in which exhaustion of the abnormally low levels of C1 esterase inhibitor results in C1 activation, breakdown of C2 and C4, and subsequent acute edema of subcutaneous tissue, the gastrointestinal tract, or the upper respiratory tract. The disease responds to attenuated androgens. Because 15% of C1 inhibitor deficiencies have nonfunctional protein, some patients will have abnormal functional results (FC1EQ / C1 Esterase Inhibitor, Functional Assay, Serum) in the presence of normal (or elevated) antigen levels.

**Useful For:** Diagnosis of hereditary angioedema Monitoring levels of C1 esterase inhibitor in response to therapy

**Interpretation:** Abnormally low results are consistent with a heterozygous C1 esterase inhibitor deficiency and hereditary angioedema. Fifteen percent of hereditary angioedema patients have a normal or elevated level but nonfunctional C1 esterase inhibitor protein. Detection of these patients requires a functional measurement of C1 esterase inhibitor; FC1EQ / C1 Esterase Inhibitor, Functional Assay, Serum. Measurement of C1q antigen levels; C1Q / Complement C1q, Serum, is key to the differential diagnoses of acquired or hereditary angioedema. Those patients with the hereditary form of the disease will have normal levels of C1q, while those with the acquired form of the disease will have low levels. Studies in children show that adult levels of C1 inhibitor are reached by 6 months of age.

**Reference Values:**  
19-37 mg/dL


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**FC1EQ 81493**

**C1 Esterase Inhibitor, Functional Assay, Serum**

**Clinical Information:** C1 inhibitor (C1-INH) is a multispecific, protease inhibitor that is present in normal human plasma and serum, and which regulates enzymes of the complement, coagulation, fibrinolytic, and kinin-forming systems. The enzymes (proteases) regulated by this protein include the C1r
and C1s subunits of the activated first component of complement, activated Hageman factor (factor Xla), kallikrein (Fletcher factor), and plasmin. A deficiency of functionally active C1-INH may lead to life-threatening angioedema. Two major forms of C1-INH deficiency have been reported: the congenital form, termed hereditary angioedema (HAE), and the acquired form that is associated with a variety of diseases, including lymphoid malignancies. HAE is characterized by transient but recurrent attacks of nonpruritic swelling of various tissues throughout the body. The symptomatology depends upon the organs involved. Intestinal attacks lead to a diversity of symptoms including pain, cramps, vomiting, and diarrhea. The most frequent cause of death in this disease is airway obstruction secondary to laryngeal edema occurring during an attack. There are 2 types of HAE that can be distinguished biochemically. Patients with the more common type (85% of HAE patients) have low levels of functional C1-INH and C1-INH antigen. Patients with the second form (15% of HAE patients) have low levels of functional C1-INH but normal or increased levels of C1-INH antigen that is dysfunctional. The variable nature of the symptoms at different time periods during the course of the disease makes it difficult to make a definitive diagnosis based solely on clinical observation.

**Useful For:** Diagnosing hereditary angioedema and for monitoring response to therapy

**Interpretation:** Hereditary angioedema (HAE) can be definitely diagnosed by laboratory tests demonstrating a marked reduction in C1 inhibitor (C1-INH) antigen or abnormally low functional C1-INH levels in a patient's plasma or serum that has normal or elevated antigen. Nonfunctional results are consistent with HAE. Patients with current attacks will also have low C2 and C4 levels due to C1 activation and complement consumption. Patients with acquired C1-INH deficiency have a low C1q in addition to low C1-INH.

**Reference Values:**
- >67% normal (normal)
- 41-67% normal (equivocal)
- <41% normal (abnormal)

**Clinical References:**

### C1Q Binding Assay

**Reference Values:**
C1Q Binding Assay 0.0 - 3.9 ugE/mL

Less than 4 ugE/mL is considered negative for circulating complement binding immune complexes.

Circulating immune complexes may be found without any evident pathology and positive results do not necessarily implicate the immune complex in a disease process.

### C1q Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (or mannan binding protein, [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex. The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1-C4) result in an inability to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or generate lytic activity. These patients have increased susceptibility to infections with encapsulated...
microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Inherited deficiency of C1 is rare. C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus [SLE], polymyositis, glomerulonephritis, and Henoch-Schönlein purpura), and SLE is the most common manifestation of C1 deficiency. The SLE associated with C1 deficiency is similar to SLE without complement deficiency, but the age of onset is often prior to puberty. Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton's and common variable hypogammaglobulinemia and severe combined immunodeficiency), and this is most likely due to increased catabolism. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of first component of complement (C1) deficiency
Investigation of a patient with an absent total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). The measurement of C1q activity is an indicator of the amount of first component of complement (C1) present. Absent C1q levels in the presence of normal C3 and C4 values are consistent with a C1 deficiency. Low C1q levels in the presence of low C4 but normal C3 may indicate the presence of an acquired inhibitor (autoantibody) to C1 esterase inhibitor.

**Reference Values:**
34-63 U/mL

**Clinical References:**

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**C2AG**

**Clinical Information:**

**Useful For:**

**Interpretation:**

**Reference Values:**
1.1-3.0 mg/dL

**Clinical References:**

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**C2FXN**

**Clinical Information:** The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. This activation process results in the formation of the lytic membrane attack complex, as well as the generation of activation peptides that are chemotactic for neutrophils and that bind to immune complexes and complement

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receptors. The absence of early components (C1, C2, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophodema, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement (CH50) of nearly zero, with normal values for C3 and C4.

**Useful For:** The investigation of a patient with a low (absent) hemolytic complement (CH50)

**Interpretation:** Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

**Reference Values:**
25-47 U/mL


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**C2 Complement, Functional, with Reflex, Serum**

**Clinical Information:** The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. This activation process results in the formation of the lytic membrane attack complex, as well as the generation of activation peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The absence of early components (C1, C2, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, and complement deficiency may be an etiologic factor in the development of autoimmune disease. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophodema, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement (CH50) of nearly zero, with normal values for C3 and C4.

**Useful For:** The investigation of a patient with a low (absent) hemolytic complement (CH50)

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent
(or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

**Reference Values:**
25-47 U/mL


### C3 Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. C3 is at the entry point for all 3 activation pathways to activate the MAC. C3 deficiency may result in pneumococcal and neisserial infections as well as autoimmune diseases such as glomerulonephritis. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C3 / Complement C3, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C3 deficiency Investigation of a patient with undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C3 levels in the presence of other normal complement values are consistent with a C3 deficiency.

**Reference Values:**
21-50 U/mL


### C3a Level

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
C4 Acylcarnitine, Quantitative, Urine

**Clinical Information:** An isolated elevation of iso-/butyrylcarnitine (C4) in plasma or newborn screening blood spots is related to a diagnosis of either short chain acyl-CoA dehydrogenase (SCAD) deficiency or isobutyryl-CoA dehydrogenase (IBD) deficiency. Diagnostic testing, including the evaluation of C4 excretion in urine, is necessary to differentiate the 2 clinical entities. Patients with IBD deficiency excrete an abnormal amount of C4 acylcarnitine in urine, whereas patients with SCAD deficiency can have a normal excretion of this metabolite. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For further information, see http://www.acmg.net. See Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma C4 acylcarnitine elevation) in Special Instructions for additional information.

**Useful For:** Evaluation of patients with abnormal newborn screens showing elevations of iso-/butyrylcarnitine (C4) to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies

**Interpretation:** Almost all patients with isobutyryl-CoA dehydrogenase deficiency excrete an abnormal amount of iso-/butyrylcarnitine (C4) in their urine. Some, but not all, affected individuals also excrete elevated levels of isobutyrylglycine. Conversely, patients with short-chain acyl-CoA dehydrogenase deficiency can have a normal excretion of C4. See Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma C4 acylcarnitine elevation) in Special Instructions for additional information.

**Reference Values:**
<3.00 millimoles/mole creatinine

**Clinical References:**

C4 Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary for clearance of immune complexes and to attract neutrophils or to generate to lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Approximately 20 cases of C4 deficiency have been reported. Most of these patients have systemic lupus erythematosus (SLE) or glomerulonephritis. Patients with C4 deficiency may also have frequent bacterial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C4 / Complement C4, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C4 deficiency Investigation of a patient with an undetectable total
Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (e.g., as a consequence of infectious or autoimmune processes). Absent C4 levels in the presence of normal C3 and C2 values are consistent with a C4 deficiency. Normal results indicate both normal C4 protein levels and normal functional activity. In hereditary angioedema, a disorder caused by C1 esterase inhibitor deficiency, absent or low C4 and C2 values are seen in the presence of normal C3 (due to activation and consumption of C4 and C2).

Reference Values:
22-45 U/mL

Clinical References:

C5 Complement, Antigen, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein, [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an absent total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (e.g., as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggests complement consumption. A small number of cases have been described in which the complement protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency C5FX / C5 Complement, Functional, Serum).

Reference Values:
10.6-26.3 mg/dL

C5 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC and may have increased susceptibility to neisserial infections. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C5AG / C5 Complement, Antigen, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an undetectable total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggest complement consumption. Normal results indicate both normal C5 protein levels and normal functional activity.

Reference Values:
29-53 U/mL


C5-DC Acylcarnitine, Quantitative, Urine

Clinical Information: An isolated elevation of glutarylcarnitine (C5-DC) in plasma or newborn screening blood spots is related to a diagnosis of glutaric aciduria type 1 (GA-1), also known as glutaric acidemia type I. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase. Follow-up testing is necessary for confirmation. Urinary excretion of C5-DC is a specific biochemical marker of GA-1 that appears to be elevated even in low excretors, affected patients with normal levels of glutaric acid in urine. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Many affected individuals also have macrocephaly. Dietary treatment and aggressive interventions during time of illness are recommended to try to prevent or minimize neurologic injury, which is most likely to occur in infancy and early childhood. Prevalence is approximately 1 in 100,000 individuals. The American College of Medical Genetics (ACMG) newborn
screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see URL: http://www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of C5-DC

**Diagnosis of glutaric aciduria type 1 deficiency**

**Interpretation:** Elevated excretion of C5-DC is a specific biochemical marker of glutaric aciduria type 1 that is elevated in affected patients, apparently even in low excretors or those affected individuals with normal levels of glutaric acid in urine.

**Reference Values:**
<1.54 millimoles/mole creatinine


---

**C5OHU 88830**

**C5-OH Acylcarnitine, Quantitative, Urine**

**Clinical Information:** The differential diagnosis of an isolated elevation of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) in plasma or (newborn screening) blood spots includes the following disorders: -3-Methylcrotonyl-CoA carboxylase deficiency (common name: 3-methylcrotonylglycinuria), either infantile or maternal -3-Hydroxy 3-methylglutaryl-(HMG)-CoA lyase deficiency -Beta-ketothiolase deficiency -2-Methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency, 3-methylglutaconic aciduria type I, and biotinidase deficiency or holocarboxylase deficiency

Confirmaatory and diagnostic testing are necessary to differentiate these clinical entities. This test can be useful in differentiating patients with 3-methylcrotonylglycinuria and with 3-methylglutaconic aciduria as they typically excrete larger amounts of C5-OH in urine compared to patients with the other diagnoses. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had positive newborn screening results. For more information, see URL: http://www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of 3-hydroxyisovaleryl-/2-methyl-3-hydroxybutyryl-carnitine (C5-OH)

**Interpretation:** Preliminary data showed that an elevated excretion in urine and concentration in plasma of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) can be the only biochemical abnormalities in patients with 3-methylcrotonylglycinuria. Contact Mayo Medical Laboratories for assistance in test interpretation and additional testing options.

**Reference Values:**
<2.93 millimoles/mole creatinine


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**C6FX 83393**

**C6 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC,
and may have increased susceptibility to neisserial infections. A number of patients with C6 deficiency have been reported, and the majority of these patients are South African. Most of these patients have systemic meningococcal infection and some have had invasive gonococcal infections. Normal levels of C6 antigen have been reported in patients with dysfunctional C6 lytic activity.

**Useful For:** Diagnosis of C6 deficiency Investigation of a patient with an undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C6 levels in the presence of normal C3 and C4 values are consistent with a C6 deficiency. Absent C6 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C6 protein levels and normal functional activity.

**Reference Values:**
32-57 U/mL

**Clinical References:**

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**C7 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein; MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. The majority of cases of C7 deficiency have neisserial infections, but cases of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, and pyoderma gangrenosum have been reported. The pathogenesis of the rheumatic disease is not clear. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C7 deficiency Investigation of a patient with an undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C7 levels in the presence of normal C3 and C4 values are consistent with a C7 deficiency. Absent C7 levels in the presence of low C3 and C4 values suggest complement consumption.

**Reference Values:**
36-60 U/mL

**Clinical References:**
**C8 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are three pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Most patients with C8 deficiency have invasive neisserial infections. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C8 deficiency Investigation of a patient with an undetectable total hemolytic complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (e.g., as a consequence of infectious or autoimmune processes). Absent C8 levels in the presence of normal C3 and C4 values are consistent with a C8 deficiency. Absent C8 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C8 protein levels and normal functional activity.

**Reference Values:**
33-58 U/mL

**Clinical References:**

**C9 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are three pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC,
and may have increased susceptibility to neisserial infections. C9 deficiency is common in the Japanese population and has been reported to occur in almost 1% of the population. The lytic activity of C9-deficient serum is decreased. However, the assembly of C5b-C8 complexes will result in a transmembrane channel with lytic activity, although the lytic activity is reduced. Many C9-deficient patients are therefore asymptomatic. C9-deficient patients may, however, present with invasive neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C9 deficiency Investigation of a patient with a low total (hemolytic) complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C9 levels in the presence of normal C3 and C4 values are consistent with a C9 deficiency. Absent C9 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C9 protein levels and normal functional activity.

**Reference Values:**
37-61 U/mL

**Clinical References:**

**C9orf72 Hexanucleotide Repeat, Molecular Analysis**

**Clinical Information:** Frontotemporal dementia (FTD) is a presenile dementia that affects the frontal and temporal lobes of the brain. Clinical presentation is variable and includes progressive changes in behavior and personality and language disturbances. Affected individuals may also exhibit extrapyramidal signs. Amyotrophic lateral sclerosis (ALS) is a progressive neurologic disease affecting the upper and lower motor neurons. The disease is characterized by progressive spasticity, muscle wasting and paralysis, typically leading to death from respiratory failure. ALS and FTD are now thought to represent an overlapping spectrum of disease. Recent literature has found that approximately 40% of familial ALS and FTD cases have a large hexanucleotide repeat (GGGGCC) expansion in a noncoding region of C9orf72.

**Useful For:** Molecular confirmation of clinically suspected cases of c9FTD/ALS, frontotemporal dementia (FTD), or amyotrophic lateral sclerosis (ALS) Presymptomatic testing for individuals with a family history of c9FTD/ALS and a documented expansion in the C9orf72 gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles: <20 GGGGCC repeats
Intermediate alleles: 20-29 GGGGCC repeats
Full penetrance: >29* GGGGCC repeats

*Alleles greater than 30 repeats are outside the reportable range for this assay and are detected using the companion Southern blot assay. There is not enough information at this time to determine if 30 repeats is the cutoff for pathogenicity.

An interpretive report will be provided.

C9FU

C9orf72, Follow Up Analysis

Reference Values:
Not applicable
Only orderable as a reflex. For more information see C9ORF / C9orf72 Hexanucleotide Repeat, Molecular Analysis.

FCABB

Cabbage IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

CABB

Cabbage, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Equivocal values apply to all ages.


**Cocoa/Cocoa, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
CDOMB
89539

Cadmium for Occupational Monitoring, Blood

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Tobacco smoke is another common source of cadmium exposure.

Useful For: Detecting exposure to cadmium, a toxic heavy metal

Interpretation: Normal blood cadmium is <5.0 mcg/L, with most results in the range of 0.5 to 2.0 mcg/L. Acute toxicity will be observed when the blood level exceeds 50 mcg/L.

Reference Values:
0.0-4.9 mcg/L

Reference values apply to all ages.


CDOM
80595

Cadmium for Occupational Monitoring, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede over renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

Useful For: Monitoring occupational exposure to cadmium

Interpretation: Cadmium excretion >3.0 mcg/g creatinine indicates significant exposure to cadmium. Results >15 mcg/g creatinine are considered indicative of severe exposure.

Reference Values:
<3.0 mcg/g

**Cadmium, 24 Hour, Urine**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Another common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal leading to reproductive toxicity in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in some patients exposed to cadmium. See also CDOM / Cadmium for Occupational Monitoring, Urine. If employees are being monitored in the workplace, the Occupational Safety and Health Administration requires that laboratory reports express the cadmium excretion rate per gram of creatinine rather than per 24 hours. This alternative test is available to accommodate that requirement. Mayo Medical Laboratories is certified to provide this test.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal

**Reference Values:**

0-15 years: not established
> or =16 years: 0.0-1.3 mcg/specimen


**Cadmium, Blood**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal

**Interpretation:** Normal blood cadmium is <5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL.

**Reference Values:**

0.0-4.9 ng/mL
Reference values apply to all ages.


### Cadmium, Random, Urine

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminophenolic acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Another common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal leading to reproductive toxicity in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in some patients exposed to cadmium. See also CDOM / Cadmium for Occupational Monitoring, Urine. If employees are being monitored in the workplace, the Occupational Safety and Health Administration requires that laboratory reports express the cadmium excretion rate per gram of creatinine rather than per liter. This alternative test is available to accommodate that requirement. Mayo Medical Laboratories is certified to provide this test.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal

**Reference Values:**

- 0-15 years: not established
- > or =16 years: 0.0-1.3 mcg/L

**Clinical References:**


### Caffeine, Serum

**Clinical Information:** Caffeine is used to treat apnea that occurs in newborn infants, the most frequent complication seen in the neonatal nursery. Caffeine is administered orally (nasogastric tube) as a loading dose of 3 mg/kg followed by a maintenance dose of 1 mg/kg administered once every 24 to 48 hours, depending on the patient's response and the serum level. In neonates, caffeine has a half-life that ranges from 20 to 100 hours, which is much longer than in adults (typically 4-6 hours) due to the immaturity of the neonatal liver. This requires that small doses be administered at much longer intervals than would be predicted based on adult pharmacokinetics. The volume of distribution of caffeine is 0.6 L/kg and the drug is approximately 35% protein bound. Toxicity observed in neonates is characterized by central nervous system and skeletal muscle stimulation and bradycardia. These symptoms are seen in adults at lower levels than in neonates, suggesting that neonates have much greater tolerance to the drug.

**Useful For:** Monitoring therapy in neonates Assessing toxicity in neonates

**Interpretation:** Optimal pharmacologic response occurs when the serum level is in the range of 8.0 to 20.0 mcg/mL. Toxicity in neonates and adults may be seen when the serum level is >20.0 mcg/mL.

**Reference Values:**

- Therapeutic: 8.0-20.0 mcg/mL
Critical value: $>30.0 \, \text{mcg/mL}$

**Clinical References:** Ou CN, Frawley VL: Concurrent measurement of theophylline and caffeine in neonates by an interference-free liquid-chromatographic method. Clin Chem 1983;29:1934-1936

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**CAH Pediatric Profile 5: 17,20 Desmolase Deficiency**

*Androstene-dione, Cortisol, DHEA, 17-OH-Prenenolone, Progesterone, 17-Alpha-Hydroxyprogesterone, Testosterone*

**Reference Values:**

Androstenedione, Mass Spec

<table>
<thead>
<tr>
<th>Units: ng/dL</th>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premature (26-28w) Day 4</td>
<td>63 - 935</td>
</tr>
<tr>
<td></td>
<td>Premature (31-35w) Day 4</td>
<td>50 - 449</td>
</tr>
<tr>
<td></td>
<td>Full Term (1 week)</td>
<td>&lt;10 - 279</td>
</tr>
</tbody>
</table>

Levels decrease rapidly to <52 ng/dL after one week.

1m-11m

$<10 - 37$

Androstenedione gradually decreases during the first six months to prepubertal levels.

<table>
<thead>
<tr>
<th>Prepubertal Children</th>
<th>&lt;10 - 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>44 - 186</td>
</tr>
<tr>
<td>Adult Females</td>
<td>28 - 230</td>
</tr>
<tr>
<td>Females Postmenopausal</td>
<td>&lt;10 â€“ 93</td>
</tr>
</tbody>
</table>

**Tanner Stages**

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.2</td>
<td>&lt;10 - 17</td>
</tr>
<tr>
<td>2</td>
<td>9.2-13.7</td>
<td>&lt;10 - 72</td>
</tr>
<tr>
<td>3</td>
<td>10.0-14.4</td>
<td>50 - 170</td>
</tr>
<tr>
<td>4</td>
<td>10.7-15.6</td>
<td>47 - 208</td>
</tr>
<tr>
<td>5</td>
<td>11.8-18.6</td>
<td>50 - 224</td>
</tr>
</tbody>
</table>

Males

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;10 - 17</td>
</tr>
<tr>
<td>2</td>
<td>9.8-14.5</td>
<td>&lt;10 - 33</td>
</tr>
<tr>
<td>3</td>
<td>10.7-15.4</td>
<td>17 - 72</td>
</tr>
<tr>
<td>4</td>
<td>11.8-16.2</td>
<td>15 - 115</td>
</tr>
<tr>
<td>5</td>
<td>12.8-17.3</td>
<td>33 - 192</td>
</tr>
</tbody>
</table>

Cortisol, Serum or Plasma

<table>
<thead>
<tr>
<th>Units: ug/dL</th>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premature (26-28w) Day 4</td>
<td>1.0 - 11</td>
</tr>
<tr>
<td></td>
<td>Premature (31-35w) Day 4</td>
<td>2.5 - 9.1</td>
</tr>
<tr>
<td></td>
<td>Full Term Day 3</td>
<td>1.7 - 14</td>
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<tr>
<td></td>
<td>Full Term Day 7</td>
<td>2.0 - 11</td>
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<tr>
<td></td>
<td>31d - 11m</td>
<td>2.8 - 23</td>
</tr>
<tr>
<td></td>
<td>12m - 15y (8:00 AM)</td>
<td>3.0 - 21</td>
</tr>
</tbody>
</table>

Adults

| 8:00 AM      | 8.0 - 19 |

---
Dehydroepiandrosterone (DHEA), Serum
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 yrs</td>
<td>&lt;68</td>
</tr>
<tr>
<td>6-7 yrs</td>
<td>&lt;111</td>
</tr>
<tr>
<td>8-10 yrs</td>
<td>&lt;186</td>
</tr>
<tr>
<td>11-12 yrs</td>
<td>&lt;202</td>
</tr>
<tr>
<td>13-14 yrs</td>
<td>&lt;319</td>
</tr>
<tr>
<td>15-16 yrs</td>
<td>39-481</td>
</tr>
<tr>
<td>17-19 yrs</td>
<td>40-491</td>
</tr>
<tr>
<td>20-49 yrs</td>
<td>31-701</td>
</tr>
<tr>
<td>&gt; or = 50 yrs</td>
<td>21-402</td>
</tr>
</tbody>
</table>

17-OH Pregnenolone, Mass Spec
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>375 - 3559</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>64 - 2380</td>
</tr>
<tr>
<td>3 Days</td>
<td>10 - 829</td>
</tr>
<tr>
<td>1 - 5m</td>
<td>36 - 763</td>
</tr>
<tr>
<td>6 - 11m</td>
<td>42 - 540</td>
</tr>
<tr>
<td>12 - 23m</td>
<td>14 - 207</td>
</tr>
<tr>
<td>24m - 5y</td>
<td>10 - 103</td>
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<tr>
<td>6 - 9y</td>
<td>10 - 186</td>
</tr>
<tr>
<td>Pubertal</td>
<td>44 - 235</td>
</tr>
<tr>
<td>Adults</td>
<td>53 - 357</td>
</tr>
</tbody>
</table>

Progesterone, Serum
Units: ng/dL

Males

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>1-16y</td>
<td>&lt;10-15</td>
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Females

<table>
<thead>
<tr>
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<tr>
<td>11y</td>
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<td>12y</td>
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<td>13y</td>
<td>&lt;10-693</td>
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<tr>
<td>14y</td>
<td>&lt;10-1204</td>
</tr>
<tr>
<td>15y</td>
<td>&lt;10-1076</td>
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<tr>
<td>16y</td>
<td>&lt;10-1294</td>
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Adult

<table>
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<tr>
<th>Cycle Days</th>
<th>Range</th>
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<tbody>
<tr>
<td>1-6</td>
<td>&lt;10-17</td>
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<tr>
<td>7-12</td>
<td>&lt;10-135</td>
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<tr>
<td>13-15</td>
<td>&lt;10-1563</td>
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<tr>
<td>16-28</td>
<td>&lt;10-2555</td>
</tr>
<tr>
<td>Post Menopausal</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Note: Luteal progesterone peaked from 350 to 3750 ng/dL on days ranging from 17 to 23.

17-Alpha-Hydroxyprogesterone, Serum
Units: ng/dL
Age                                         Range
Premature (26-28w) Day 4                    124 - 841
Premature (31-35w) Day 4                    26 - 568
Full-Term Day 3                             <78

Males: Levels increase after the first week to peak values ranging from 40 - 200 between 30 and 60 days. Values then decline to a prepubertal value of <91 before one year.

Prepubertal <91
Adult Males 27 - 199

Females

1 - 11m  13 - 106
Prepubertal <91

Adolescent Females

Follicular 15 - 70
Luteal 35 – 290

Testosterone, Serum (Total)
Units: ng/dL
Age                                         Range
Males
Premature (26-28w) Day 4                    59 - 125
Premature (31-35w) Day 4                    37 - 198
Newborns                                     75 - 400

1 - 7m: Levels decrease rapidly the first week to 20 - 50, then increase to 60 - 400 between 20 - 60 days. Levels then decline to prepubertal range levels of <2.5 - 10 by seven months.

Females

Premature (26 - 28w) Day 4                    5 - 16
Premature (31 - 35w) Day 4                    5 - 22
Newborns                                      20 - 64

1 - 7m: Levels decrease during the first month to less than 10 and remain there until puberty.

Prepubertal Males and Females <2.5 - 10
Adult Males >18 years                         348 - 1197
Adult Females
### Males

<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Age (years)</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;2.5 - 10</td>
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<tr>
<td>2</td>
<td>9.8 - 14.5</td>
<td>18 - 150</td>
</tr>
<tr>
<td>3</td>
<td>10.7 - 15.4</td>
<td>100 - 320</td>
</tr>
<tr>
<td>4</td>
<td>11.8 - 16.2</td>
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</tr>
<tr>
<td>5</td>
<td>12.8 - 17.3</td>
<td>350 - 970</td>
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### Females

<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Age (years)</th>
<th>Female</th>
</tr>
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<tr>
<td>2</td>
<td>9.2 - 13.7</td>
<td>7 - 28</td>
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<tr>
<td>3</td>
<td>10.0 - 14.4</td>
<td>15 - 35</td>
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<tr>
<td>4</td>
<td>10.7 - 15.6</td>
<td>13 - 32</td>
</tr>
<tr>
<td>5</td>
<td>11.8 - 18.6</td>
<td>20 - 38</td>
</tr>
</tbody>
</table>

---

**CAH Pediatric Profile 1, 21-OH Deficiency Screen**  
*Androstene-dione, Cortisol, DHEA, 17-OH-Progesterone, Testosterone*

**Reference Values:**

**Androstenedione, Mass Spec**  
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>63-935</td>
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<tr>
<td>Premature (31-35w) Day 4</td>
<td>50-449</td>
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<tr>
<td>Full Term (1-7 days)</td>
<td>&lt;10-279</td>
</tr>
</tbody>
</table>

Levels decrease rapidly to <52 ng/dL after one week.  
1m-11m <10-37

Androstenedione gradually decreases during the first six months to prepubertal levels.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal Children</td>
<td>&lt;10-17</td>
</tr>
<tr>
<td>Adult Males</td>
<td>44-186</td>
</tr>
<tr>
<td>Adult Females</td>
<td>28-230</td>
</tr>
<tr>
<td>Females Postmenopausal</td>
<td>&lt;10-93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.2</td>
<td>&lt;10-17</td>
</tr>
<tr>
<td>2</td>
<td>9.2 - 13.7</td>
<td>&lt;10-72</td>
</tr>
<tr>
<td>3</td>
<td>10.0 - 14.4</td>
<td>50-170</td>
</tr>
<tr>
<td>4</td>
<td>10.7 - 15.6</td>
<td>47-208</td>
</tr>
<tr>
<td>5</td>
<td>11.8 - 18.6</td>
<td>50-224</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Males Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;10-17</td>
</tr>
<tr>
<td>2</td>
<td>9.8 - 14.5</td>
<td>&lt;10-33</td>
</tr>
<tr>
<td>3</td>
<td>10.7 - 15.4</td>
<td>17-72</td>
</tr>
<tr>
<td>4</td>
<td>11.8 - 16.2</td>
<td>15-115</td>
</tr>
<tr>
<td>5</td>
<td>12.8 - 17.3</td>
<td>33-192</td>
</tr>
</tbody>
</table>
Cortisol, Serum or Plasma  
Units: ug/dL  

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>1.0 - 11</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>2.5 - 9.1</td>
</tr>
<tr>
<td>Full Term Day 3</td>
<td>1.7 - 14</td>
</tr>
<tr>
<td>Full Term Day 7</td>
<td>2.0 - 11</td>
</tr>
<tr>
<td>31d - 11m</td>
<td>2.8 - 23</td>
</tr>
<tr>
<td>12m - 15y (8:00 AM)</td>
<td>3.0 - 21</td>
</tr>
</tbody>
</table>

Adults  
8:00 AM  
4.0 - 19  
4:00 PM  
4.0 - 11

Dehydroepiandrosterone (DHEA), Serum  
Units: ng/dL  

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 yrs</td>
<td>&lt;68</td>
</tr>
<tr>
<td>6-7 yrs</td>
<td>&lt;111</td>
</tr>
<tr>
<td>8-10 yrs</td>
<td>&lt;186</td>
</tr>
<tr>
<td>11-12 yrs</td>
<td>&lt;202</td>
</tr>
<tr>
<td>13-14 yrs</td>
<td>&lt;319</td>
</tr>
<tr>
<td>15-16 yrs</td>
<td>39-481</td>
</tr>
<tr>
<td>17-19 yrs</td>
<td>40-491</td>
</tr>
<tr>
<td>20-49 yrs</td>
<td>31-701</td>
</tr>
<tr>
<td>&gt; or = 50 yrs</td>
<td>21-402</td>
</tr>
</tbody>
</table>

17-AIpha-Hydroxyprogesterone, Serum  
Units: ng/dL  

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>124 - 841</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>26 - 568</td>
</tr>
<tr>
<td>Full-Term Day 3</td>
<td>&lt;78</td>
</tr>
</tbody>
</table>

Males: Levels increase after the first week to peak values ranging from 40 - 200 between 30 and 60 days. Values then decline to a prepubertal value of <91 before one year.

Prepubertal  
<91  
Adult Males  
27 - 199

Females  
1 - 11m  
13 - 106  
Prepubertal  
<91  
Adult Females  
Follicular  
15 - 70  
Luteal  
35 - 290

Females  
Tanner Stages  
Age (years)  
Range  
1  
<9.2  
<83  
2  
9.2-13.7  
11-98  
3  
10.0-14.4  
11-155  
4  
10.7-15.6  
18-230  
5  
11.8-18.6  
20-265  

Males
Tanner Stages | Age (years) | Range
--- | --- | ---
1 | <9.8 | <91
2 | 9.8-14.5 | <116
3 | 10.7-15.4 | 10-138
4 | 11.8-16.2 | 29-180
5 | 12.8-17.3 | 24-175

Testosterone, Serum (Total)
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>59 - 125</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>37 - 198</td>
</tr>
<tr>
<td>Newborns</td>
<td>75 - 400</td>
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</tbody>
</table>

1 - 7m: Levels decrease rapidly the first week to 20 - 50, then increase to 60 - 400 between 20 - 60 days. Levels then decline to prepubertal range levels of <2.5 - 10 by seven months.

Females
| Premature (26 - 28w) Day 4 | 5 - 16 |
| Premature (31 - 35w) Day 4 | 5 - 22 |
| Newborns | 20 - 64 |

1 - 7m: Levels decrease during the first month to less than 10 and remain there until puberty.

Prepubertal Males and Females | <2.5 - 10 |
Adult Males >18 years | 348 - 1197 |
Adult Females
- Premenopausal: | 10 - 55 |
- Postmenopausal: | 7 - 40 |
Males
Tanner Stage | Age (years) | Male
--- | --- | ---
1 | <9.8 | <2.5 α€“ 10
2 | 9.8 α€“ 14.5 | 18 α€“ 150
3 | 10.7 α€“ 15.4 | 100 α€“ 320
4 | 11.8 α€“ 16.2 | 200 α€“ 620
5 | 12.8 α€“ 17.3 | 350 α€“ 970

Females
Tanner Stage | Age (years) | Female
--- | --- | ---
1 | <9.2 | <2.5 α€“ 10
2 | 9.2 α€“ 13.7 | 7 α€“ 28
3 | 10.0 α€“ 14.4 | 15 α€“ 35
4 | 10.7 α€“ 15.6 | 13 α€“ 32
5 | 11.8 α€“ 18.6 | 20 - 38
Levels decrease rapidly to <52 ng/dL after one week.

Androstenedione gradually decreases during the first six months to prepubertal levels.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal Children</td>
<td>&lt;10-17</td>
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<tr>
<td>Adult Males</td>
<td>44-186</td>
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<tr>
<td>Adult Females</td>
<td>28-230</td>
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<td>Females Postmenopausal</td>
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### Tanner Stages

<table>
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<th>Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
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<tbody>
<tr>
<td>1</td>
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<td>&lt;10-17</td>
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<tr>
<td>2</td>
<td>9.2-13.7</td>
<td>&lt;10-72</td>
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<th>Tanner Stages</th>
<th>Age (years)</th>
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<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;10-17</td>
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<td>2</td>
<td>9.8-14.5</td>
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<td>4</td>
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<td>5</td>
<td>12.8-17.3</td>
<td>33-192</td>
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### Cortisol

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Range</th>
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<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>1.0 - 11</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>2.5 - 9.1</td>
</tr>
<tr>
<td>Full Term Day 3</td>
<td>1.7 - 14</td>
</tr>
<tr>
<td>Full Term Day 7</td>
<td>2.0 - 11</td>
</tr>
<tr>
<td>31d - 11m</td>
<td>2.8 - 23</td>
</tr>
<tr>
<td>12m - 15y (8:00 AM)</td>
<td>3.0 - 21</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Range</th>
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<tbody>
<tr>
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### Dehydroepiandrosterone (DHEA)

<table>
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<th>Age Group</th>
<th>Range</th>
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<tbody>
<tr>
<td>1-5 yrs</td>
<td>&lt;68</td>
</tr>
<tr>
<td>6-7 yrs</td>
<td>&lt;111</td>
</tr>
<tr>
<td>8-10 yrs</td>
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<td>31-701</td>
</tr>
<tr>
<td>&gt; or = 50 yrs</td>
<td>21-402</td>
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### 17-OH Pregnenolone

<table>
<thead>
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<th>Range</th>
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<tbody>
<tr>
<td>17-OH Pregnenolone</td>
<td>21-402</td>
</tr>
<tr>
<td>Age</td>
<td>Range</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>375 - 3559</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>64 - 2380</td>
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<tr>
<td>3 Days</td>
<td>10 - 829</td>
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<tr>
<td>1 - 5m</td>
<td>36 - 763</td>
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<td>6 - 11m</td>
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<td>14 - 207</td>
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<td>24m - 5y</td>
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<tr>
<td>6 - 9y</td>
<td>10 - 186</td>
</tr>
<tr>
<td>Pubertal</td>
<td>44 - 235</td>
</tr>
<tr>
<td>Adults</td>
<td>53 - 357</td>
</tr>
</tbody>
</table>

17-Alphahydroxyprogesterone

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>124 - 841</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>26 - 568</td>
</tr>
</tbody>
</table>

(if no age submitted):

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-Term Day 3</td>
<td>&lt;78</td>
</tr>
</tbody>
</table>

Males: Levels increase after the first week to peak values ranging from 40 - 200 between 30 and 60 days. Values then decline to a prepubertal value of <91 before one year.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>&lt;91</td>
</tr>
<tr>
<td>Adult Males</td>
<td>27 - 199</td>
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Females

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Prepubertal</td>
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</tr>
<tr>
<td>Adult Females</td>
<td>13 - 106</td>
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</table>

<table>
<thead>
<tr>
<th>Age</th>
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</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>15 - 70</td>
</tr>
<tr>
<td>Luteal</td>
<td>35 - 290</td>
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</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
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<tr>
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<td>&lt;83</td>
</tr>
<tr>
<td>2</td>
<td>9.2-13.7</td>
<td>11-98</td>
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<tr>
<td>3</td>
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Males

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<td>5</td>
<td>12.8-17.3</td>
<td>24-175</td>
</tr>
</tbody>
</table>

CAH Pediatric Profile 6, Comprehensive Screen
(Androstenedione, Specific S, Cortisol, DHEA, DOC, 17-OH-Prenenolone, Progesterone, 17-OH-Progesterone, Testosterone)

Reference Values:
Androstenedione
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>63 - 935</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>50 - 449</td>
</tr>
<tr>
<td>Full Term (1-7 days)</td>
<td>&lt;10 - 279</td>
</tr>
</tbody>
</table>

Levels decrease rapidly to a range of <52 ng/dL after one week.

1-11m                                      | <10 - 37 |

Androstenedione gradually decreases during the first six months to prepubertal levels.

<table>
<thead>
<tr>
<th>Prepubertal Children</th>
<th>&lt;10-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>44 - 186</td>
</tr>
<tr>
<td>Adult Females</td>
<td>28 - 230</td>
</tr>
<tr>
<td>Females Postmenopausal</td>
<td>&lt;10-93</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.2</td>
<td>&lt;10-17</td>
</tr>
<tr>
<td>9.2-13.7</td>
<td>&lt;10-72</td>
</tr>
<tr>
<td>10.0-14.4</td>
<td>50-170</td>
</tr>
<tr>
<td>10.7-15.6</td>
<td>47-208</td>
</tr>
<tr>
<td>11.8-18.6</td>
<td>50-224</td>
</tr>
</tbody>
</table>

Males

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.8</td>
<td>&lt;10-17</td>
</tr>
<tr>
<td>9.8-14.5</td>
<td>&lt;10-33</td>
</tr>
<tr>
<td>10.7-15.4</td>
<td>17-72</td>
</tr>
<tr>
<td>11.8-16.2</td>
<td>15-115</td>
</tr>
<tr>
<td>12.8-17.3</td>
<td>33-192</td>
</tr>
</tbody>
</table>

Cortisol

Units: ug/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>1.0 - 11</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>2.5 - 9.1</td>
</tr>
<tr>
<td>Full Term Day 3</td>
<td>1.7 - 14</td>
</tr>
<tr>
<td>Full Term Day 7</td>
<td>2.0 - 11</td>
</tr>
<tr>
<td>31d - 11m</td>
<td>2.8 - 23</td>
</tr>
<tr>
<td>12m - 15y (8:00 AM)</td>
<td>3.0 - 21</td>
</tr>
</tbody>
</table>

Adults

<table>
<thead>
<tr>
<th>Time</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>8.0 - 19</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>4.0 - 11</td>
</tr>
</tbody>
</table>

Deoxycorticosterone (DOC)

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 28w) Day 4</td>
<td>20 - 105</td>
</tr>
<tr>
<td>Premature (34 - 36w) Day 4</td>
<td>28 - 78</td>
</tr>
<tr>
<td>Newborn: Levels are markedly elevated at birth and decrease rapidly during the first week to the range of 7 - 49 as found in older infants.</td>
<td></td>
</tr>
<tr>
<td>1 - 11m</td>
<td>7 - 49</td>
</tr>
<tr>
<td>Prepubertal Children</td>
<td>2 - 34</td>
</tr>
</tbody>
</table>
### Dehydroepiandrosterone (DHEA)

**Units:** ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 yrs</td>
<td>&lt;68</td>
</tr>
<tr>
<td>6-7 yrs</td>
<td>&lt;111</td>
</tr>
<tr>
<td>8-10 yrs</td>
<td>&lt;186</td>
</tr>
<tr>
<td>11-12 yrs</td>
<td>&lt;202</td>
</tr>
<tr>
<td>13-14 yrs</td>
<td>&lt;319</td>
</tr>
<tr>
<td>15-16 yrs</td>
<td>39-481</td>
</tr>
<tr>
<td>17-19 yrs</td>
<td>40-491</td>
</tr>
<tr>
<td>20-49 yrs</td>
<td>31-701</td>
</tr>
<tr>
<td>&gt; or = 50 yrs</td>
<td>21-402</td>
</tr>
</tbody>
</table>

### 11-Desoxycortisol

**Units:** ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>110 - 1376</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>48 - 579</td>
</tr>
<tr>
<td>Newborn Day 3</td>
<td>13 - 147</td>
</tr>
<tr>
<td>1 - 11m</td>
<td>&lt;10 - 156</td>
</tr>
<tr>
<td>Prepubertal 8:00 AM</td>
<td>20 - 155</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>12 - 158</td>
</tr>
</tbody>
</table>

### 17-OH Pregnenolone

**Units:** ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>375 - 3559</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>64 - 2380</td>
</tr>
<tr>
<td>3 Days</td>
<td>10 - 829</td>
</tr>
<tr>
<td>1 - 5m</td>
<td>36 - 763</td>
</tr>
<tr>
<td>6 - 11m</td>
<td>42 - 540</td>
</tr>
<tr>
<td>12 - 23m</td>
<td>14 - 207</td>
</tr>
<tr>
<td>24m - 5y</td>
<td>10 - 103</td>
</tr>
<tr>
<td>6 - 9y</td>
<td>10 - 186</td>
</tr>
<tr>
<td>Pubertal</td>
<td>44 - 235</td>
</tr>
<tr>
<td>Adults</td>
<td>53 - 357</td>
</tr>
</tbody>
</table>

### Progesterone

**Units:** ng/dL

<table>
<thead>
<tr>
<th>Males</th>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-16y</td>
<td>&lt;10-15</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>&lt;10-11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females</th>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-10y</td>
<td>&lt;10-26</td>
</tr>
<tr>
<td></td>
<td>11y</td>
<td>&lt;10-255</td>
</tr>
<tr>
<td></td>
<td>12y</td>
<td>&lt;10-856</td>
</tr>
<tr>
<td></td>
<td>13y</td>
<td>&lt;10-693</td>
</tr>
<tr>
<td></td>
<td>14y</td>
<td>&lt;10-1204</td>
</tr>
<tr>
<td></td>
<td>15y</td>
<td>&lt;10-1076</td>
</tr>
<tr>
<td></td>
<td>16y</td>
<td>&lt;10-1294</td>
</tr>
<tr>
<td>Adult Cycle Days</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>1-6</td>
<td>&lt;10-17</td>
<td></td>
</tr>
<tr>
<td>7-12</td>
<td>&lt;10-135</td>
<td></td>
</tr>
<tr>
<td>13-15</td>
<td>&lt;10-1563</td>
<td></td>
</tr>
<tr>
<td>16-28</td>
<td>&lt;10-2555</td>
<td></td>
</tr>
<tr>
<td>Post Menopausal</td>
<td>&lt;10</td>
<td></td>
</tr>
</tbody>
</table>

Note: Luteal progesterone peaked from 350 to 3750 ng/dL on days ranging from 17 to 23.

17-Angle-Hydroxyprogesterone

<table>
<thead>
<tr>
<th>Units: ng/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Premature (26-28w) Day 4</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
</tr>
<tr>
<td>Full-Term Day 3</td>
</tr>
</tbody>
</table>

Males: Levels increase after the first week to peak values ranging from 40 - 200 between 30 and 60 days. Values then decline to a prepubertal value of <91 before one year.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.2</td>
<td>&lt;91</td>
</tr>
<tr>
<td>9.2-13.7</td>
<td>11-98</td>
</tr>
<tr>
<td>10.0-14.4</td>
<td>11-155</td>
</tr>
<tr>
<td>10.7-15.6</td>
<td>18-230</td>
</tr>
<tr>
<td>11.8-18.6</td>
<td>20-265</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.2</td>
<td>&lt;83</td>
</tr>
<tr>
<td>2</td>
<td>9.2-13.7</td>
<td>11-98</td>
</tr>
<tr>
<td>3</td>
<td>10.0-14.4</td>
<td>11-155</td>
</tr>
<tr>
<td>4</td>
<td>10.7-15.6</td>
<td>18-230</td>
</tr>
<tr>
<td>5</td>
<td>11.8-18.6</td>
<td>20-265</td>
</tr>
</tbody>
</table>

Males

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;91</td>
</tr>
<tr>
<td>2</td>
<td>9.8-14.5</td>
<td>&lt;116</td>
</tr>
<tr>
<td>3</td>
<td>10.7-15.4</td>
<td>10-138</td>
</tr>
<tr>
<td>4</td>
<td>11.8-16.2</td>
<td>29-180</td>
</tr>
<tr>
<td>5</td>
<td>12.8-17.3</td>
<td>24-175</td>
</tr>
</tbody>
</table>

Testosterone, Serum (Total)

<table>
<thead>
<tr>
<th>Units: ng/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Premature (26-28w) Day 4</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
</tr>
<tr>
<td>Newborns</td>
</tr>
</tbody>
</table>

1 - 7m: Levels decrease rapidly the first week to 20 - 50, then increase to 60 - 400 between 20 - 60 days. Levels then decline to prepubertal range levels of 2.5 - 10 by seven months.
Females
- Premature (26 - 28w) Day 4: 5 - 16
- Premature (31 - 35w) Day 4: 5 - 22
- Newborns: 20 - 64

1 - 7m: Levels decrease during the first month to less than 10 and remain there until puberty.

Prepubertal Males and Females: <2.5 - 10
Adult Males (>18 years): 348 - 1197
Adult Females
- Premenopausal: 10 - 55
- Postmenopausal: 7 - 40

Males
<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Age (years)</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;2.5 - 10</td>
</tr>
<tr>
<td>2</td>
<td>9.8 - 14.5</td>
<td>18 - 150</td>
</tr>
<tr>
<td>3</td>
<td>10.7 - 15.4</td>
<td>100 - 320</td>
</tr>
<tr>
<td>4</td>
<td>11.8 - 16.2</td>
<td>200 - 620</td>
</tr>
<tr>
<td>5</td>
<td>12.8 - 17.3</td>
<td>350 - 970</td>
</tr>
</tbody>
</table>

Females
<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Age (years)</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.2</td>
<td>&lt;2.5 - 10</td>
</tr>
<tr>
<td>2</td>
<td>9.2 - 13.7</td>
<td>7 - 28</td>
</tr>
<tr>
<td>3</td>
<td>10.0 - 14.4</td>
<td>15 - 35</td>
</tr>
<tr>
<td>4</td>
<td>10.7 - 15.6</td>
<td>13 - 32</td>
</tr>
<tr>
<td>5</td>
<td>11.8 - 18.6</td>
<td>20 - 38</td>
</tr>
</tbody>
</table>

### Calcitonin, Fine-Needle Aspiration Biopsy (FNAB)-Needle Wash, Lymph Node

**Clinical Information:** Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C-cells) of the thyroid gland. Malignant tumors arising from thyroid C-cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising <5% of all thyroid malignancies. Measurement of serum calcitonin is used in the follow-up of patients who underwent surgical removal of the thyroid gland. Studies have reported that the measurement of calcitonin in fine-needle aspiration biopsy (FNAB)-needle washes improves the evaluation of suspicious lymph nodes in patients with a history of MTC when used in combination with cytology. Comparing the results of calcitonin in the needle rinse with serum calcitonin is highly recommended. An elevated calcitonin in the serum could falsely elevate calcitonin in the washings, if the rinse is contaminated with blood. In these cases only calcitonin values significantly higher than the serum should be considered as true-positives. Cytologic examination and measurement of calcitonin can be performed on the same specimen. To measure calcitonin, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination (for a smear or CytoTrap preparation) has been expelled from the needle. Calcitonin levels are measured in the needle wash.

**Useful For:** As an adjunct to cytologic examination of fine-needle aspiration specimens in athyrotic individuals treated for medullary thyroid carcinoma to confirm or exclude metastases in enlarged or ultrasonographically suspicious lymph nodes

**Interpretation:** In athyrotic patients with a history of medullary thyroid carcinoma (MTC), a fine-needle aspiration calcitonin value \( \geq 5.0 \) pg/mL is suggestive of the presence of metastatic MTC in the biopsied lymph node.

**Reference Values:**
An interpretive report will be provided.


**Calcitonin, Serum**

**Clinical Information:** In the normal physiological situation, calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C cells) of the thyroid gland. The main action of calcitonin is the inhibition of bone resorption by regulating the number and activity of osteoclasts. Calcitonin is secreted in direct response to serum hypercalcemia and may prevent large oscillations in serum calcium levels and excessive loss of body calcium. However, in comparison to parathyroid hormone and 1,25-dihydroxyvitamin D, the role of calcitonin in the regulation of serum calcium in humans is minor. Measurements of serum calcitonin levels are, therefore, not useful in the diagnosis of disorders of calcium homeostasis. Malignant tumors arising from thyroid C cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising <5% of all thyroid malignancies. Approximately 25% of these cases are familial, usually appearing as a component of multiple endocrine neoplasia type II (MENII, Sipple syndrome). MTC may also occur in families without other associated endocrine dysfunction, with similar autosomal dominant transmission as MENII, which is then called familial medullary thyroid carcinoma (FMTC). Mutations in the RET proto-oncogene are associated with MENII and FMTC. Other neuroendocrine tumors and islet cell tumors may, also produce calcitonin, but do so much less frequently. Calcitonin elevations also may occur with: -Cancer of the lung, breast, or pancreas -Intestinal, gastric, or bronchial carcinoids -Chronic renal failure, Zollinger-Ellison syndrome, or pernicious anemia -Pregnant females at term -Newborns

**Useful For:** Diagnosis and follow-up of medullary thyroid carcinoma Adjunct to diagnosis of multiple endocrine neoplasia type II and familial medullary thyroid carcinoma Occasionally useful in the diagnosis and follow-up of islet cell tumors

**Interpretation:** Although most patients with sporadic medullary thyroid carcinoma (MTC) have high basal calcitonin levels, 30% of those with familial MTC or multiple endocrine neoplasia type II (MENII) have normal basal levels. In the past, these individuals may have required a calcium infusion provocative test (short calcium infusion with blood drawing at 0, 5, and 10 minutes) to demonstrate the abnormality. Mutation screening (MENMS / Multiple Endocrine Neoplasia Type 2 [2A, 2B, FMTC] Mutation Screen) of RET has largely superseded calcium infusion provocative testing. Calcium infusion tests are now only necessary in suspected familial cases belonging to 1 of the 5% to 10% of MEN/FMTC (multiple endocrine neoplasia/familial medullary thyroid carcinoma) families without detectable RET mutations. For these rare cases, the Mayo Clinic Endocrine Testing Unit should be consulted for additional information on the short calcium infusion test, including necessary precautions. In completely cured cases following surgical therapy for MTC, serum calcitonin levels fall into the undetectable range over a variable period of several weeks. Persistently elevated postoperative serum calcitonin levels usually indicate incomplete cure. The reasons for this can be locoregional lymph node spread or distant metastases. In most of these cases, imaging procedures are required for further workup. Those individuals who are then found to suffer only locoregional spread may benefit from additional surgical procedures. However, the survival benefits derived from such approaches are still debated. A rise in previously undetectable or very low postoperative serum calcitonin levels is highly suggestive of disease recurrence or spread, and should trigger further diagnostic evaluations.

**Reference Values:**

**BASAL**

Males: <16 pg/mL
Females: <8 pg/mL
**PEAK CALCIUM INFUSION**

Males: < or =130 pg/mL

Females: < or =90 pg/mL

**Clinical References:**

---

**CALU**

**Calcium, 24 Hour, Urine**

**Clinical Information:** Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

**Useful For:**
- Evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturations
- Evaluation of bone diseases, including osteoporosis and osteomalacia

**Interpretation:** Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is >250 mg in men and >200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

**Reference Values:**
Males: <250 mg/24 hours
Females: <200 mg/24 hours

Reference values have not been established for patients <18 years and >83 years of age. Reference values apply to 24-hour collection.

**Clinical References:**

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**CAI**

**Calcium, Ionized, Serum**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Clinical Information**: Ionized calcium, which accounts for 50% to 55% of total calcium, is the physiologically active form of calcium. Low ionized calcium values are often seen in renal disease, critically ill patients, or patients receiving rapid transfusion of citrated whole blood or blood products. Increased serum ionized calcium concentrations may be seen with primary hyperparathyroidism, ectopic parathyroid hormone-producing tumors, excess intake of vitamin D, or various malignancies. Nomograms have been used to calculate ionized calcium from total calcium, albumin, and pH values. However, calculated ionized calcium results have proven to be unsatisfactory. A Mayo study of 114 patients found significant differences between ionized and total calcium in 26% of patients.

**Useful For**: Assessing calcium states during liver transplantation surgery, cardiopulmonary bypass, or any procedure requiring rapid transfusion of whole blood in neonates and in critically ill patients

**Second-order test in the evaluation of patients with abnormal calcium values**

**Interpretation**: Serum ionized calcium concentrations 50% below normal result in severely reduced cardiac stroke work. With moderate to severe hypocalemia, left ventricular function may be profoundly depressed. Ionized calcium values are higher in children and young adults. Ionized calcium values vary inversely with pH, approximately 0.2 mg/dL per 0.1 pH unit change.

**Reference Values**:

### Males
- 1-19 years: 5.1-5.9 mg/dL
- > or =20 years: 4.8-5.7 mg/dL

Reference values have not been established for patients that are <12 months of age.

### Females
- 1-17 years: 5.1-5.9 mg/dL
- > or =18 years: 4.8-5.7 mg/dL

Reference values have not been established for patients that are <12 months of age.


---

**CACR1 63450 Calcium, Random, Urine**

**Clinical Information**: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

**Useful For**: Evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturations Evaluation of bone diseases, including osteoporosis and osteomalacia

**Interpretation**: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed “idiopathic”). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is >250 mg in men and >200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine
calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

**Reference Values:**
Random Calcium/Creatinine Ratio: <0.20 mg/mg

Reference values have not been established for patients < 18 years and > 83 years of age.

**Clinical References:**

**CACR2 36882 Calcium, Random, Urine**

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR Supersaturation Profile, Pediatric, Random, Urine.

**CAS 8432 Calcium, Total, Serum**

**Clinical Information:** The calcium content of an adult is somewhat over 1 kg (about 2% of the body weight). Of this, 99% is present as calcium hydroxyapatite in bones and < 1% is present in the extra-osseous intracellular space or extracellular space (ECS). The calcium level in the ECS is in dynamic equilibrium with the rapidly exchangeable fraction of bone calcium. In serum, calcium is bound to a considerable extent to proteins (approximately 40%), 10% is in the form of inorganic complexes, and 50% is present as free or ionized calcium. Calcium ions affect the contractility of the heart and the skeletal musculature, and are essential for the function of the nervous system. In addition, calcium ions play an important role in blood clotting and bone mineralization. Hypocalcemia is due to the absence or impaired function of the parathyroid glands or impaired vitamin-D synthesis. Chronic renal failure is also frequently associated with hypocalcemia due to decreased vitamin-D synthesis as well as hyperphosphatemia and skeletal resistance to the action of parathyroid hormone (PTH). A characteristic symptom of hypocalcemia is latent or manifest tetany and osteomalacia. Hypercalcemia is brought about by increased mobilization of calcium from the skeletal system or increased intestinal absorption. The majority of cases are due to primary hyperparathyroidism (pHPT) or bone metastasis of carcinoma of the breast, prostate, thyroid gland, or lung. Patients who have pHPT and bone disease, renal stones or nephrocalcinosis, or other signs or symptoms are candidates for surgical removal of the parathyroid gland(s). Severe hypercalcemia may result in cardiac arrhythmia. Total calcium levels also may reflect protein levels.

**Useful For:**
The diagnosis and monitoring of a wide range of disorders including diseases of bone, kidney, parathyroid gland, or gastrointestinal tract. Calcium levels may also reflect abnormal vitamin D or protein levels.

**Interpretation:** Hypocalcemia: Long-term therapy must be tailored to the specific disease causing the hypocalcemia. The therapeutic endpoint is to achieve a serum calcium level of 8.0 to 8.5 mg/dL to prevent tetany. For symptomatic hypocalcemia, calcium may be administered intravenously. Hypercalcemia: The level at which hypercalcemic symptoms occur varies from patient to patient. Symptoms are common when serum calcium levels are > 11.5 mg/dL, although patients may be asymptomatic at this level. Levels > 12.0 mg/dL are considered a critical value in the Mayo Health System. Severe hypercalcemia (> 15.0 mg/dL) is a medical emergency.

**Reference Values:**
Males
1-14 years: 9.6-10.6 mg/dL
15-16 years: 9.5-10.5 mg/dL
17-18 years: 9.5-10.4 mg/dL
19-21 years: 9.3-10.3 mg/dL
> or =22 years: 8.9-10.1 mg/dL

Reference values have not been established for patients who are <12 months of age.

Females
1-11 years: 9.6-10.6 mg/dL
12-14 years: 9.5-10.4 mg/dL
15-18 years: 9.1-10.3 mg/dL
> or =19 years: 8.9-10.1 mg/dL

Reference values have not been established for patients who are <12 months of age.

California Virus (La Crosse) IgG and IgM, Serum

**Clinical Information:** California virus (La Crosse) is a member of Bunyaviridae and is 1 of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children under 15 years of age, usually from rural areas. Incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, last 1 to 3 days, and are followed by the appearance of central nervous system signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas.

**Useful For:** Aiding the diagnosis of California virus (La Crosse)

**Interpretation:** In patients infected with these or related viruses, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG > 1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age: serious La Crosse infections primarily involve children, especially boys. Adult males exposed to La Crosse have high prevalence rates of antibody but usually show no serious illness. Infection among males is primarily due to working conditions and sports activity taking place where the vector is present.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

**Clinical References:**

Calprotectin, Feces

**Clinical Information:** Calprotectin, formed as a heterodimer of S100A8 and S100A9, is a member of the S100 calcium-binding protein family. It is expressed primarily by granulocytes, and to a lesser degree by monocytes/macrophages and epithelial cells. In neutrophils, calprotectin comprises almost 60% of the total cytoplasmic protein content. Activation of the intestinal immune system leads to recruitment of cells from the innate immune system, including neutrophils. The neutrophils are then activated, which leads to release of cellular proteins, including calprotectin. Calprotectin eventually translocates across the epithelial barrier and enters the lumen of the gut. As the inflammatory process progresses, the released calprotectin is absorbed by the fecal material before it is excreted from the body. The amount of calprotectin present in the feces is proportional to the number of neutrophils within the gastrointestinal...
mucosa, and can be used as an indirect marker of intestinal inflammation. Calprotectin is most frequently
used as part of the diagnostic evaluation of patients with suspected inflammatory bowel disease (IBD). Patients with IBD may be diagnosed with Crohn's disease or ulcerative colitis. Although distinct in their pathology and clinical manifestations, both are associated with significant intestinal inflammation. Elevated concentrations of fecal calprotectin may be useful in distinguishing IBD from functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). When used for this differential diagnosis, fecal calprotectin has sensitivity and specificity both of approximately 85%. However, it must be remembered that increases in fecal calprotectin are not diagnostic for IBD, as other disorders such as celiac disease, colorectal cancer, and gastrointestinal infections, may also be associated with neutrophilic inflammation.

**Useful For:** Evaluation of patients suspected of having a gastrointestinal inflammatory process. Distinguishing irritable bowel disease (IBD) from irritable bowel syndrome (IBS), when used in conjunction with other diagnostic modalities, including endoscopy, histology, and imaging

**Interpretation:** Calprotectin concentrations $\leq 50.0$ mcg/g are not suggestive of an active inflammatory process within the gastrointestinal system. For patients experiencing gastrointestinal symptoms, consider further evaluation for functional gastrointestinal disorders. Calprotectin concentrations between 50.1 and 120.0 mcg/g are borderline and may represent a mild inflammatory process, such as in treated irritable bowel disease (IBD) or associated with NSAID or aspirin usage. For patients with clinical symptoms suggestive of IBD, retesting in 4 to 6 weeks may be indicated. Calprotectin concentrations $> 120.1$ mcg/g are suggestive of an active inflammatory process within the gastrointestinal system. Further diagnostic testing to determine the etiology of the inflammation is suggested.

**Reference Values:**
- $\leq 50.0$ mcg/g (Normal)
- 50.1-120.0 mcg/g (Borderline)
- $> 120.1$ mcg/g (Abnormal)

**Reference values apply to all ages.**

**Clinical References:**

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**CALR**

**CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN)**

**Clinical Information:** The most frequent genetic mutation in BCR-ABL1-negative myeloproliferative neoplasm (MPN), essential thrombocythemia (ET), and primary myelofibrosis (PMF) is the JAK2V617F mutation, which is present in approximately 50% to 60% of patients. It serves as a confirmatory molecular marker of these diseases. Mutations in the MPL gene are found in an additional 5% to 10% of ET and PMF cases. It was recently discovered that somatic mutation (insertions and/or deletions) in exon 9 of the CALR gene is the second most frequent somatic mutation after JAK2 in ET and PMF patients, and it is mutually exclusive of JAK2 and MPL mutations. (1,2) It has a frequency of approximately 49% to 88% in JAK2 and MPL-wild type (WT) ET and PMF, and is not found in polycythemia vera (PV) patients. (1-4) Therefore, CALR mutation serves as an important diagnostic molecular marker in ET and PMF. The CALR gene encodes for calreticulin, a multifunctional protein with a C-terminus rich in acidic amino acids and a KDEL ER-retention motif. All the pathologic CALR mutations reported to date are out-of-frame insertion and/or deletions (indel) in exon 9, generating a 1 base-pair (bp) frame shift and a mutant protein with a novel C-terminus rich in basic amino acids and loss of the KDEL ER-retention signal. The most common mutation types are 52-bp deletion (c.1092_1143del, L367fs*46) and 5-bp insertion (c.1154_1155insTTGCC, K385fs*47), and they comprise approximately 85% of CALR mutations in MPN. (1,2) CALR mutations have been found in hematopoietic stem and progenitor cells in MPN patients (2) and may activate the STAT5 signaling pathway. (1) They are
associated with decreased risk of thrombosis in ET (1,3-5), and better survival in PMF compared to JAK2 mutations.(5)

**Useful For:** Rapid and sensitive detection of insertion and deletion-type mutations in exon 9 of CALR
An aid in distinction between reactive thrombocytosis and/or leukocytosis versus a myeloproliferative neoplasm (MPN), especially essential thrombocythemia (ET) and primary myelofibrosis (PMF), and is highly informative in cases in which JAK2 and MPL testing are negative. Especially helpful to the pathologist in those bone marrow cases with ambiguous etiology of thrombocytosis, equivocal bone marrow morphologic findings of MPN, and/or unexplained reticulin fibrosis. An aid in prognostication of PMF and thrombosis risk assessment in ET.

**Interpretation:** An interpretive report will be issued. The results will be reported as 1 of the 3 states if DNA amplification is successful (see Cautions): -Positive. A deletion/insertion-type mutation was detected in CALR, exon 9. -Negative. No deletion or insertion was detected in CALR, exon 9. -Equivocal. A small amplicon suspicious for a deletion/insertion type mutation was detected in CALR, exon 9. Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory and morphologic features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplastic disorders.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

**CALX 36997**
**CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Reflex**
**Reference Values:**
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

**FCAMP 91224**
**Campylobacter jejuni Antibody, ELISA**
**Reference Values:**
Reference Range: <0.90

Interpretive Criteria:
- <0.90 Antibody Not Detected
- 0.90-1.10 Equivocal
- >1.10 Antibody Detected

Campylobacter jejuni is a major cause of sporadic bacterial diarrhea in the United States, with poultry the most important source of infection. Markedly elevated levels of antibodies recognizing C. jejuni typically indicate recent or ongoing infection, even though stool cultures may be negative. Neurological complications may follow C. jejuni infection; approximately 30% of Guillain-Barre cases are associated with recent C. jejuni infection. The basis of this association is apparently molecular mimicry between C. jejuni antigens and gangliosides of neuronal cells.
Canary Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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</tbody>
</table>

Reference values apply to all ages.


Canary Grass, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Canavan Disease, Mutation Analysis, ASPA**

**Clinical Information:** Canavan disease is a severe leukodystrophy resulting from a deficiency of the enzyme aspartoacylase. Mutations in the ASPA gene cause the clinical manifestations of Canavan disease. The deficiency of aspartoacylase leads to spongy degeneration of the brain, and the disease is characterized by delayed development beginning at age 3 to 6 months, head lag, macrocephaly, and hypotonia. Death usually occurs within the first decade of life. The carrier rate in the Ashkenazi Jewish population is 1 in 41. Four ASPA mutations are included in this test: 433(-2)A->G, A305E, E285A, and Y231X. The E285A and Y231X mutations account for approximately 98% of the mutations in the Ashkenazi Jewish population. The A305E mutation accounts for approximately 50% of the mutations in the non-Ashkenazi Jewish population.

**Useful For:** Carrier testing for Canavan disease in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of Canavan disease in at-risk pregnancies Confirmation of a suspected clinical diagnosis of Canavan disease in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretative report will be provided.

**Reference Values:**

An interpretive report will be provided.

Cancer Antigen 125 (CA 125), Serum

**Clinical Information:** Cancer antigen 125 (CA 125) is a glycoprotein antigen normally expressed in tissues derived from coelomic epithelia (ovary, fallopian tube, peritoneum, pleura, pericardium, colon, kidney, stomach). Serum CA 125 is elevated in approximately 80% of women with advanced epithelial ovarian cancer, but assay sensitivity is suboptimal in early disease stages. The average reported sensitivities are 50% for stage I and 90% for stage II or greater. Elevated serum CA 125 levels have been reported in individuals with a variety of nonovarian malignancies including cervical, liver, pancreatic, lung, colon, stomach, biliary tract, uterus, fallopian tube, breast, and endometrial carcinomas. Elevated serum CA 125 levels have been reported in individuals with a variety of nonmalignant conditions including: cirrhosis, hepatitis, endometriosis, first trimester pregnancy, ovarian cysts, and pelvic inflammatory disease. Elevated levels during the menstrual cycle also have been reported.

**Useful For:** Evaluating patients' response to cancer therapy, especially for ovarian carcinoma 
Predicting recurrent ovarian cancer or intraperitoneal tumor

**Interpretation:** In monitoring studies, elevations of cancer antigen 125 (CA 125) >35 U/mL after debulking surgery and chemotherapy indicate that residual disease is likely (>95% accuracy). However, normal levels do not rule-out recurrence. A persistently rising CA 125 value suggests progressive malignant disease and poor therapeutic response. Physiologic half-life of CA 125 is approximately 5 days. In patients with advanced disease who have undergone cytoreductive surgery and are on chemotherapy, a prolonged half-life (>20 days) may be associated with a shortened disease-free survival.

**Reference Values:**
<35 U/mL

**Clinical References:**

Cancer Antigen 15-3 (CA 15-3), Serum

**Clinical Information:** Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens that are large molecular weight glycoproteins with O-linked oligosaccharide chains. Tumor-associated antigens encoded by the human MUC-1 gene are known by several names, including MAM6, milk mucin antigen, cancer antigen (CA) 27.29, and CA 15-3. CA 15-3 assay values are not elevated in most normal individuals and are frequently elevated in sera from breast cancer patients. Nonmammary malignancies in which elevated CA 15-3 assay values have been reported include: lung, colon, pancreas, primary liver, ovary, cervix, and endometrium.

**Useful For:** Managing breast cancer patients when used in conjunction with clinical information and other diagnostic procedures. Serial testing can assist in early detection of disease recurrence in previously treated stage II and III breast cancer patients. Monitoring response to therapy in metastatic breast cancer patients

**Interpretation:** Increasing and decreasing values show correlation with disease progression and regression, respectively. Increasing cancer antigen 15-3 (CA 15-3) assay values in patients at risk for breast cancer recurrence after primary therapy may be indicative of recurrent disease before it can be detected clinically (2,3) and may be used as an indication that additional tests or procedures should be performed.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 371
Males: <30 U/mL (use not defined)
Females: <30 U/mL


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**Candida albicans (Monilia), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Reference Range: <1.0

Interpretive Criteria:
<1.0 Antibody not detected
> or = 1.0 Antibody detected

Systemic candidiasis is often characterized by markedly elevated levels of IgG, IgA, and IgM recognizing Candida. However, interpretation of Candida antibody levels is complicated by detection of antibodies in 20-30% of healthy individuals, and blunted antibody responses in immuno-compromised patients at risk for systemic candidiasis. Candida antibody results should be considered within the context of clinical findings and results from other relevant laboratory tests, such as Candida antigen detection and/or culture.

**FCANP**
91830
Candida Antigen and Antibody Panel

**Reference Values:**
Candida Antigen Detection

REFERENCE RANGE: <1:2

INTERPRETIVE CRITERIA:
<1:2 Antigen Not Detected
> or = 1:2 Antigen Detected

Detection of Candida albicans antigen in serum is highly suggestive of systemic or disseminated candidiasis.

Candida Albicans Antibodies (IgG, IgA, IgM)

REFERENCE RANGE: <1.0

INTERPRETIVE CRITERIA:
<1.0 Antibody not detected
> or = 1.0 Antibody detected

Systemic candidiasis is often characterized by markedly elevated levels of IgG, IgA, and IgM recognizing Candida. However, interpretation of Candida antibody levels is complicated by detection of antibodies in 20-30% of healthy individuals, and blunted antibody responses in immuno-compromised patients at risk for systemic candidiasis. Candida antibody results should be considered within the context of clinical findings and results from other relevant laboratory tests, such as Candida antigen detection and/or culture.

**FCAND**
90067
Candida Antigen Detection

**Reference Values:**
REFERENCE RANGE: <1:2

INTERPRETIVE CRITERIA:
<1:2 Antigen Not Detected
> or = 1:2 Antigen Detected

Detection of Candida albicans antigen in serum is highly suggestive of systemic or disseminated candidiasis.
**Cannabinoid Analysis, Whole Blood**

**Reference Values:**

This specimen was screened by Immunoassay. Any positive result is confirmed by gas chromatography with mass spectrometry (GC/MS). The following threshold concentrations are used for this analysis:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening Threshold</th>
<th>Confirmation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoids</td>
<td>5 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Tetrahydrocannabinol</td>
<td>2 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Carboxy-THC</td>
<td>2 ng/mL</td>
<td></td>
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</tbody>
</table>

**Caraway, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Carbamazepine Hypersensitivity Pharmacogenomics, Blood

Clinical Information: Carbamazepine is sometimes prescribed for the treatment of epilepsy, as well as trigeminal neuralgia and bipolar disorder. A minority of carbamazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. More severe reactions, such as the hypersensitivity syndrome, are associated with mortality of up to 10% and include symptoms such as rash, fever, eosinophilia, hepatitis, and nephritis. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the HLA-B*15:02 allele varies throughout Asia: 10% to 15% frequency in Chinese, 2% to 4% frequency in Southeast Asians, including Indians, and <1% frequency in Japanese and Koreans. The HLA-A*31:01 allele, which has a prevalence of 2% to 5% in Northern European populations, has been significantly associated with drug-associated cutaneous adverse reactions. In the absence of HLA-A*31:01, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the HLA-B*15:02 allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of HLA-A*31:01 allele with drug-associated cutaneous adverse reactions regardless of ethnicity but does not specifically mandate screening of patients. For patients who are HLA-B*15:02 and HLA-A*31:01 positive, oxcarbazepine, phenytoin, fosphenytoin, eslicarbazepine acetate, and lamotrigine may also be associated with drug-associated cutaneous adverse reactions so these medications may need to be avoided as well.

Useful For: Identifying individuals with increased risk of risk of carbamazepine-associated cutaneous adverse reactions Identifying individuals who may be at increased risk of cutaneous adverse reactions when treated with alternative medications to carbamazepine including phenytoin, fosphenytoin, oxcarbazepine, eslicarbazepine acetate, and lamotrigine

Interpretation: The presence of the HLA-B*15:02 and/or HLA-A*31:01 allele confers increased risk for hypersensitivity to carbamazepine.

Reference Values: An interpretive report will be provided.


Carbamazepine Hypersensitivity Pharmacogenomics, Saliva

Clinical Information: Carbamazepine is sometimes prescribed for the treatment of epilepsy, as well as trigeminal neuralgia and bipolar disorder. A minority of carbamazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. More severe reactions, such as the hypersensitivity syndrome, are associated with mortality of up to 10% and include symptoms such as rash, fever, eosinophilia, hepatitis, and nephritis. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the
body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the HLA-B*15:02 allele varies throughout Asia: 10% to 15% frequency in Chinese, 2% to 4% frequency in Southeast Asians, including Indians, and <1% frequency in Japanese and Koreans. The HLA-A*31:01 allele, which has a prevalence of 2% to 5% in Northern European populations, has been significantly associated with drug-associated cutaneous adverse reactions. In the absence of HLA-A*31:01, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the HLA-B*15:02 allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of HLA-A*31:01 allele with drug-associated cutaneous adverse reactions regardless of ethnicity but does not specifically mandate screening of patients. For patients who are HLA-B*15:02 and HLA-A*31:01 positive, oxcarbazepine, phenytoin, fosphenytoin, eslicarbazepine acetate, and lamotrigine may also be associated with drug-associated cutaneous adverse reactions so these medications may need to be avoided as well.

**Useful For:** Identifying individuals with increased risk of carbamazepine-associated cutaneous adverse reactions
Identifying individuals who may be at increased risk of cutaneous adverse reactions when treated with alternative medications to carbamazepine including phenytoin, fosphenytoin, oxcarbazepine, eslicarbazepine acetate, and lamotrigine Genotyping patients who prefer not to have their blood drawn

**Interpretation:** The presence of the HLA-B*15:02 and/or HLA-A*31:01 allele confers increased risk for hypersensitivity to carbamazepine. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Carbamazepine Profile, Serum**

**Clinical Information:** Carbamazepine is a common antiepileptic drug. It is a first-line drug for treatment of partial seizures and trigeminal neuralgia. Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11), which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine high-dose carbamazepine therapy, especially in combination with the above conditions

**Useful For:** Monitoring patients exhibiting symptoms of carbamazepine toxicity whose serum
carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide.

**Interpretation:** The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually < or =0.2 mcg/mL in symptomatic adults and < or =0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

**Reference Values:**
- **CARBAMAZEPINE, TOTAL**
  - Therapeutic: 4.0-12.0 mcg/mL
  - Critical value: > or =15.0 mcg/mL

- **CARBAMAZEPINE-10,11-EPOXIDE**
  - Therapeutic: 0.4-4.0 mcg/mL
  - Toxic concentration: > or =8.0 mcg/mL

- **CARBAMAZEPINE, FREE**
  - Therapeutic: 1.0-3.0 mcg/mL
  - Critical value: > or =4.0 mcg/mL

**Clinical References:**

**Carbamazepine, Free and Total, Serum**

**Clinical Information:** Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures. It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid. Under normal circumstances, the carbamazepine that circulates in blood is 75% protein bound. In severe uremia, carbamazepine may be displaced from protein, resulting in a higher free (unbound) fraction of the drug circulating in blood. Since neurologic activity and toxicity are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine level may be useful in patients with severe uremia.

**Useful For:** Monitoring carbamazepine (free and total) therapy in uremic patients

**Interpretation:** In patients with normal renal function, optimal response is often associated with free (unbound) carbamazepine levels >1.0 mcg/mL, and toxicity may occur when the free carbamazepine is > or =4.0 mcg/mL. In uremic patients, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free levels. Toxicity may occur in these patients when the free carbamazepine level is > or =4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. They are best used as a guide in dose adjustment.

**Reference Values:**
- **CARBAMAZEPINE, TOTAL**
  - Therapeutic: 4.0-12.0 mcg/mL
Carbamazepine, Free, Serum

Clinical Information: Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures. It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid. Under normal circumstances, the carbamazepine that circulates in blood is 75% protein-bound. In severe uremia, carbamazepine may be displaced from protein resulting in a higher free (unbound) fraction of the drug circulating in blood. Since neurologic activity and toxicity of carbamazepine are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine level may be useful in patients with severe uremia.

Useful For: Monitoring carbamazepine (free) therapy in uremic patients

Interpretation: In patients with normal renal function, optimal response is often associated with free (unbound) carbamazepine levels >1.0 mcg/mL, and toxicity may occur when the free carbamazepine is > or =4.0 mcg/mL. In uremia, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free carbamazepine levels. Toxicity may occur when the free carbamazepine level is > or =4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. Serum levels are best used as a guide in dose adjustment.

Reference Values:
Therapeutic concentration: 1.0-3.0 mcg/mL
Critical value: > or =4.0 mcg/mL

**Carbamazepine, Total, Serum**

**Clinical Information:** Carbamazepine (Tegretol) is used in the control of partial seizures with both temporal lobe and psychomotor symptoms, and for generalized tonic-clonic seizures. It is also used for analgesia in trigeminal neuralgia. Carbamazepine exhibits a volume of distribution of 1.4 L/kg with an elimination half-life of 15 hours. Protein binding averages 75%. Carbamazepine-10,11-epoxide (CBZ10-11) is an active metabolite that represents the predominant form of the drug in children. The volume of distribution of CBZ10-11 is 1.1 L/kg, and the half-life is 8 hours. Aplastic anemia and agranulocytosis are rare side effects of treatment with carbamazepine; baseline hematologic data should be documented before treatment is initiated. Toxicity associated with carbamazepine overdose occurs when the blood level is ≥15.0 mcg/mL and is typified by irregular breathing, muscle irritability, and hyperreflexia; followed by hyporeflexia, tachycardia, hypotension, and impaired consciousness with coma in severe toxicity; the higher the blood level, the more severe the symptoms.

**Useful For:** Monitoring therapy Determining compliance Assessing toxicity

**Interpretation:** Dosage adjustments are usually guided by monitoring blood levels. Most patients respond well when the serum concentration is in the range of 4.0 to 12.0 mcg/mL. Toxicity often occurs when levels are ≥15.0 mcg/mL.

**Reference Values:**
- Therapeutic: 4.0-12.0 mcg/mL
- Critical value: ≥15.0 mcg/mL

**Clinical References:**

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**Carbamazepine-10,11-Epoxide, Serum**

**Clinical Information:** Carbamazepine is a common antiepileptic drug. It is a first-line drug for treatment of partial seizures and trigeminal neuralgia. Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11) which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: - Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) - Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine - High-dose carbamazepine therapy, especially in combination with the above conditions

**Useful For:** Monitoring patients exhibiting symptoms of carbamazepine toxicity whose serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide

**Interpretation:** The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually < or =0.2 mcg/mL in symptomatic adults and < or =0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

**Reference Values:**
- CARBAMAZEPINE, TOTAL Therapeutic: 4.0-12.0 mcg/mL Critical value: > or =15.0 mcg/mL
- CARBAMAZEPINE-10,11-EPOXIDE Therapeutic concentration: 0.4-4.0 mcg/mL Toxic concentration: > or =8.0 mcg/mL

**Clinical References:**

**HODGE**

Carbapenemase Detection, Modified Hodge Test

**Clinical Information:** Resistance to antibiotic therapy via production of the enzyme carbapenemase by Klebsiella pneumoniae and other members of Enterobacteriaceae is becoming more common. This resistance is not always detected by conventional antimicrobial susceptibility testing, which may result in inappropriate antimicrobial therapy for the patient. In Enterobacteriaceae, the gene blaKPC, which encodes KPC (Klebsiella pneumoniae carbapenemase) production, can be detected by real-time PCR. However, molecular methods have not been established for other carbapenemases. The modified Hodge test, a phenotypic method, is recommended by the Clinical and Laboratory Standards Institute (CLSI) as the method to detect carbapenemases.

**Useful For:** Determining carbapenem resistance

**Interpretation:** A positive result indicates the production of carbapenemase. A negative result indicates the lack of production of carbapenemase.

**Reference Values:**

Negative

**Clinical References:** The 2009 CLSI Standards for Antimicrobial Susceptibility Testing. CLSI Audioconference. Janet Hindler. Original air date: January 21, 2009

**CARNP**

Carbapenemase Detection-Carba NP Test

**Clinical Information:** Gram-negative bacilli (GNB) with acquired carbapenemases have disseminated worldwide, rendering them a global threat. The therapeutic armamentarium for infections caused by carbapenem-resistant Enterobacteriaceae (CRE) is limited, and CRE infections have been associated with significant mortality. Enterobacteriaceae harboring Klebsiella pneumoniae carbapenemase are endemic in some regions of the United States, and although still sporadic, GNB harboring New Delhi metallo-beta-lactamase have been reported from several states. Timely detection of these carbapenemases (along with emerging carbapenemases such as OXA-48 and VIM) is important. Detection is challenging since isolates may have only borderline reductions in susceptibility to carbapenems, and carbapenem resistance may be mediated by mechanisms other than carbapenemases (eg, AmpC or extended-spectrum beta-lactamase with decreased membrane permeability). While molecular methods are confirmatory, testing may not be immediately available and may be limited by the number of targets assayed. The modified Hodge test suffers from lack of specificity, a long turnaround time, and poor sensitivity for metallo-beta-lactamase detection. The Carba NP test is preferred over the modified Hodge test due to improved specificity and faster turnaround time. The Carba NP test is more specific than and as sensitive as the carbapenemase-modified Hodge test. If an isolate is suspected to possess KPC or NDM carbapenemase (eg, due to local epidemiology), KPC and NDM PCR (KPNRP / KPC (blaKPC) and NDM (blaNDM) in Gram-Negative Bacilli, Molecular Detection, PCR) may be preferred over the Carba NP test.

**Useful For:** Confirmation of carbapenemase production from pure isolates of Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter species

**Interpretation:** A positive result indicates production of a carbapenemase by the isolate submitted for testing. A negative result indicates lack of production of a carbapenemase by the isolate submitted for
testing.

**Reference Values:**
Negative


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**Carbapenemase Detection-Carba NP Test (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

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**Carbohydrate Antigen 19-9 (CA 19-9), Pancreatic Cyst Fluid**

**Clinical Information:** Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen, and has been used as a tumor marker. Serum CA 19-9 concentrations may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, colon cancer, or pancreatic cancer. While serum CA 19-9 is neither sensitive nor specific for pancreatic cancer, concentrations of CA 19-9 in pancreatic cyst fluid may help determine whether a pancreatic cyst is benign. Cystic lesions of the pancreas are of various types: -Benign cysts: - Inflammatory cysts (pseudocysts) - Serous cysts (serous cystadenoma) - Mucinous cysts: - Premalignant (mucinous cystadenoma) - Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia) Pancreatic cyst fluid CA 19-9 results should be used in conjunction with imaging studies, cytology, and other cyst-fluid tumor markers, such as carcinoembryonic antigen and amylase.

**Useful For:** As an adjunct in the assessment of pancreatic cysts, when used in conjunction with carcinoembryonic antigen, amylase, imaging studies and cytology

**Interpretation:** Cyst fluid carbohydrate antigen 19-9 (CA19-9) concentrations < or =37 U/mL indicate a low risk for a mucinous cyst, and are more consistent with serous cystadenoma or pseudocyst. The sensitivity and specificity are approximately 19% and 98%, respectively, at this concentration. Correlation of these test results with cytology and imaging is recommended.

**Reference Values:**
An interpretive report will be provided.


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**Carbohydrate Antigen 19-9 (CA 19-9), Peritoneal Fluid**

**Clinical Information:** Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylosus ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of
malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in the serum patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Measurement of CA 19-9 in ascitic fluid is sometimes used in combination with cytology for detecting malignancy-related ascites.

**Useful For:** An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

**Interpretation:** A peritoneal fluid carbohydrate antigen 19-9 (CA 19-9) concentration >32 U/mL is suspicious, but not diagnostic, of a malignancy-related ascites. This clinical decision limit cutoff yielded 44% sensitivity and 93% specificity in a study of 137 patients presenting with ascites. However, ascites caused by malignancies not associated with increase serum CA 19-9 concentrations, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations <32 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CA 19-9 levels in serum.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Carbohydrate Antigen 19-9 (CA 19-9), Pleural Fluid**

**Clinical Information:** Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, requiring cytological examination of the fluid. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology findings. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. Healthy adults typically produce low to undetectable levels of CA 19-9. Serum concentrations of CA 19-9 may be elevated in patients with certain malignancies that secrete CA 19-9 into circulation, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. Pleural fluid concentrations of CA 19-9 have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CA 19-9 and elevate serum CA 19-9 concentrations, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers, typically also elevate CA 19-9 in pleural fluid. In contrast, malignancies that do not secrete CA 19-9, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CA 19-9 in pleural fluid comparable to concentrations observed in nonmalignant effusions. CA 19-9 results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

**Useful For:** An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

**Interpretation:** A pleural fluid carbohydrate antigen 19-9 (CA 19-9) concentration of > or =20.0 U/mL is suspicious, but not diagnostic, of a malignant source of the effusion. This cutoff yielded a sensitivity of 35%, specificity of 95%, and positive predictive value of 88% in a study of 200 patients presenting with effusion. CA 19-9 concentrations were significantly higher in effusions caused by CA 19-9-secreting malignancies, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian,
and pancreatic cancers. However, effusions caused by non-CA 19-9-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations <20.0 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CA 19-9-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CA19 9288**

**Carbohydrate Antigen 19-9 (CA 19-9), Serum**

**Clinical Information:** Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Benign conditions such as cirrhosis, cholestasis, and pancreatitis also result in elevated serum CA 19-9 concentrations but in these cases values usually are <1,000 U/mL. Individuals that are Lewis negative (5%-7% of the population) do not express CA 19-9 due to the lack of the enzyme fucosyltransferase needed for CA 19-9 production. In these individuals, a low or undetectable serum CA 19-9 concentration is not informative regarding cancer recurrence.

**Useful For:** Potentially useful adjunct for diagnosis and monitoring of pancreatic cancer May be used for differentiating patients with cholangiocarcinoma and primary sclerosing cholangitis (PSC) from those with PSC alone

**Interpretation:** Serial monitoring of carbohydrate antigen 19-9 (CA 19-9) should begin prior to therapy to verify post-therapy decreases in CA 19-9 and to establish a baseline for evaluating possible recurrence. Single values of CA 19-9 are less informative. Elevated values may be caused by a variety of malignant and nonmalignant conditions including cholangiocarcinoma, pancreatic cancer, and/or colon cancer.

**Reference Values:**
<55 U/mL
Serum markers are not specific for malignancy, and values may vary by method.

**Clinical References:**

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**CDG 89891**

**Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum**

**Clinical Information:** Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of over 75 inherited metabolic disorders affecting several steps of the pathway involved in the glycosylation of proteins. CDG are currently classified into 2 main groups. Type I CDG is characterized by defects in the assembly or transfer of the dolichol-linked glycan, while type II involves processing defects of the glycan. Apolipoprotein CIII (Apo-CIII) isoforms, a protein with a single core 1 mucin type O-glycosylate protein, is a complementary evaluation for the CDG type II profile. This analysis will evaluate mucin type O-glycosylation, a defect that happens in the Golgi apparatus, and will change the ratios, increasing the asialo or monoisalo forms and decreasing the fully sialilate (distal) forms. CDG typically present as multisystemic disorders with a broad clinical spectrum including developmental delay, hypotonia, with or without neurological abnormalities, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases ranging from a mild presentation...
in adults to severe multiorgan dysfunctions causing infantile lethality. In some subtypes, MPI-CDG (CDG-Ib) in particular, intelligence is not compromised. CDG should be suspected in all patients with neurological abnormalities including developmental delay and seizures, brain abnormalities such as cerebellar atrophy or hypoplasia as well as unexplained liver dysfunction. Abnormal subcutaneous fat distribution and chronic diarrhea each may or may not be present. The differential diagnosis of abnormal transferrin patterns also includes liver disease not related to CDG including uncontrolled galactosemia, hereditary fructose intolerance in acute crisis, and liver disease of unexplained etiology. Transferrin and apolipoprotein CIII isoform analysis test is the initial screening test for CDG. The results of the transferrin and apolipoprotein CIII isoform analysis should be correlated with the clinical presentation to determine the most appropriate follow-up testing strategy including enzyme, molecular, and research-based testing. Enzymatic analysis for phosphomannomutase and phosphomannose isomerase in leukocytes (PMMIL / Phosphomannomutase [PMM] and Phosphomannose Isomerase [PMI], Leukocytes) or fibroblasts (PMMIF / Phosphomannomutase [PMM] and Phosphomannose Isomerase [PMI], Fibroblasts) should be performed if either PMM2-CDG (CDG-Ia) or MPI-CDG (CDG-Ib) are suspected.

**Useful For:** Screening for congenital disorders of glycosylation

**Interpretation:** Positive test results could be due to a genetic or nongenetic condition; additional confirmatory testing is required. Results are reported as the mono-oligosaccharide/di-oligosaccharide transferrin ratio, the a-oligosaccharide/di-oligosaccharide transferrin ratio, the tri-sialo/di-oligosaccharide transferrin ratio, and the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio, and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio. The report will include the quantitative results and an interpretation. The congenital disorders of glycosylation (CDG) profiles are categorized in 4 types: 
- CDG type I profile. Mono-oligosaccharide/di-oligosaccharide transferrin ratio, and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio are abnormal. This group should have the apolipoprotein C-III profile within the normal ranges, because the Golgi system is not affected in CDG type I. 
- CDG type II profile. The tri-sialo/di-oligosaccharide transferrin ratio is abnormal. In this category, the apolipoprotein C-III profile will have 2 scenarios: 
  - The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio will be abnormal when the defect is most likely glycan processing in the Golgi apparatus, therefore the CDG defect is likely. 
  - The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio are normal, in this case most likely the defects do not involve the Golgi system, thus the molecular defect is different. 
- CDG mixed type profile (type I and II together). In this type of profile one can have abnormal tri-sialo/di-oligosaccharide transferrin ratio with the mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio abnormal, and may have the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio normal or abnormal, depending if the defects involve Golgi apparatus. When the profile cannot be categorized following the above classification, all the abnormal transferrin and/or Apo-CIII species will be reported descriptively according to the molecular mass stating the possible structures. Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to more precisely identify the correct form of CDG. Treatment options, the name and telephone number of contacts who may provide studies at Mayo Clinic or elsewhere, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided.

**Reference Values:**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Normal</th>
<th>Indeterminate</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin Mono-oligo/Di-oligo Ratio</td>
<td>&lt; or =0.06 0.07-0.09</td>
<td>&gt; or =0.10</td>
<td></td>
</tr>
<tr>
<td>Transferrin A-oligo/Di-oligo Ratio</td>
<td>&lt; or =0.011 0.012-0.021</td>
<td>&gt; or =0.022</td>
<td></td>
</tr>
<tr>
<td>Transferrin Tri-sialo/Di-oligo Ratio</td>
<td>&lt; or =0.05 0.06-0.12</td>
<td>&gt; or =0.13</td>
<td></td>
</tr>
<tr>
<td>Apo CIII-1/Apo CIII-2 Ratio</td>
<td>&lt; or =2.91 2.92-3.68</td>
<td>&gt; or =3.69</td>
<td></td>
</tr>
<tr>
<td>Apo CIII-0/Apo CIII-2 Ratio</td>
<td>&lt; or =0.48 0.49-0.68</td>
<td>&gt; or =0.69</td>
<td></td>
</tr>
</tbody>
</table>

**CDTA 82425**

**Carbohydrate Deficient Transferrin, Adult, Serum**

**Clinical Information:** Chronic alcoholism causes a transient change in the glycosylation pattern of transferrin where the relative amounts of disialo- and asialotransferrin (carbohydrate deficient transferrin: CDT) are increased over the amount of normally glycosylated tetrasialotransferrin. This recognition led to the use of CDT in serum as marker for chronic alcohol abuse. CDT typically normalizes within several weeks of abstinence of alcohol use. However, it is important to recognize that there are other causes of abnormal CDT levels, which include congenital disorders of glycosylation and other genetic and non-genetic causes of acute or chronic liver disease. CDT testing alone is not recommended for general screening for alcoholism; however, when combined with other methods (ie, gamma-glutamyltransferase, mean corpuscular volume, patient self-reporting, ethylglucuronide analysis) clinicians can expect to identify the majority of patients who consume a large amount of alcohol.

**Useful For:** An indicator of chronic alcohol abuse

**Interpretation:** Patients with chronic alcoholism may develop abnormally glycosylated transferrin isoforms (ie, carbohydrate deficient transferring: CDT >0.12). CDT results from 0.11 to 0.12 are considered indeterminate. Patients with liver disease due to genetic or nongenetic causes may also have abnormal results.

**Reference Values:**
- < or =0.10
- 0.11-0.12 (indeterminate)

**Clinical References:**

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**CHOU 9255**

**Carbohydrate, Urine**

**Clinical Information:** Saccharides (also called carbohydrates) are a group of mono-, di-, and oligosaccharides of endogenous and exogenous sources. Their presence frequently reflects dietary consumption, but can indicate specific pathology if either a particular saccharide or a particular excretory pattern is present. Most saccharides (except glucose) have low renal thresholds and are readily excreted in the urine. The presence of saccharides in urine is seen in some inborn errors of metabolism. Urine tests for reducing substances (eg, copper reduction test) are often used to screen for those disorders. However, in addition to sugars, a number of other substances present in biological fluids (eg, salicylates, uric acid, hippuric acid, ascorbic acid) have reducing properties. Conversely, some saccharides such as sucrose and trehalose do not have reducing properties. Other saccharides present at low concentrations may not be identified by reducing tests. Substances in urine may inhibit glucose oxidase-based tests and, also, other saccharides of diagnostic importance may be present along with glucose in urine. Chromatography of urinary saccharides is, therefore, required in many instances to identify the particular species of saccharide present. Any specimen tested for urinary carbohydrates is concurrently tested for the presence of succinyl nucleosides to screen for inborn errors of purine synthesis.

**Useful For:** Screening for disorders with increased excretion of fructose, glucose, galactose,
Disaccharides, oligosaccharides, and succinylpurines

**Interpretation:** The saccharide(s) present is named, identification of the probable source, and an interpretive comment is provided.

**Reference Values:**
Negative
If positive, carbohydrate is identified.


**Carbon Monoxide, Blood**

**Clinical Information:** Carbon monoxide (CO) poisoning causes anoxia, because CO binds to hemoglobin with an affinity 240 times greater than that of oxygen, thus preventing delivery of oxygen to the tissues. Twenty percent saturation of hemoglobin induces symptoms (headache, fatigue, dizziness, confusion, nausea, vomiting, increased pulse, and respiratory rate). Sixty percent saturation is usually fatal. This concentration is reached when there is 1 part CO per 1,000 parts air. Carboxyhemoglobin diminishes at a rate of about 15% per hour when the patient is removed from the contaminated environment. The most common cause of CO toxicity is exposure to automobile exhaust fumes. Significant levels of carboxyhemoglobin can also be observed in heavy smokers. Victims of fires often show elevated levels from inhaling CO generated during combustion. Susceptibility to CO poisoning is increased in anemic persons.

**Useful For:** Verifying carbon monoxide toxicity in cases of suspected exposure

**Interpretation:** Normal Concentration Non-Smokers: 0-2% Smokers: < or =9% Toxic concentration: > or =20%

**Reference Values:**
Normal Concentration
Non-Smokers: 0-2%
Smokers: < or =9%
Toxic concentration: > or =20%


**Carboxy-Tetrahydrocannabinol (THC) Confirmation, Chain of Custody, Urine**

**Clinical Information:** Delta-9-tetrahydrocannabinol is the active agent of the popularly abused street drug, marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, 1 of them being delta-9-tetrahydrocannabinol carboxylic acid. The immunochemical procedure used to screen for tetrahydrocannabinol (THC) as part of IDOAU / Drug Abuse Survey, Urine is designed to cross-react with THC carboxylic acid. In almost all medico-legal cases and in screening of employees, or when the patient adamantly denies THC use and the
immunochemical test is positive, confirmation of the result by gas chromatography-mass spectrometry and EIA are required. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana) Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of tetrahydrocannabinol carboxylic acid (THC-COOH), a major metabolite of delta-9-tetrahydrocannabinol, in urine at concentrations >15 ng/mL is a strong indicator that the patient has used marijuana. The metabolite of marijuana (THC-COOH) has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine >100 ng/mL indicates relatively recent use, probably within the past 7 days. Levels >500 ng/mL suggest chronic and recent use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

**Reference Values:**
Negative
Positives are reported with a quantitative GC-MS result.

Cutoff concentrations:
**IMMUNOASSAY SCREEN**
<50 ng/mL

**THC CARBOXYLIC ACID BY GC-MS**
<3 ng/mL


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**Carboxy-Tetrahydrocannabinol (THC) Confirmation, Urine**

**Clinical Information:** Delta-9-tetrahydrocannabinol is the active agent of the popularly abused street drug, marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid. The immunochemical procedure used to screen for tetrahydrocannabinol (THC) as part of IDOAU / Drug Abuse Survey, Urine is designed to cross-react with THC carboxylic acid. In almost all medico-legal cases and in screening of employees, or when the patient adamantly denies THC use and the immunochemical test is positive, confirmation of the result by gas chromatography-mass spectrometry (GC-MS) and EIA are required.

**Useful For:** Detection and confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana)

**Interpretation:** The presence of tetrahydrocannabinol carboxylic acid (THC-COOH), a major metabolite of delta-9-tetrahydrocannabinol, in urine at concentrations >15.0 ng/mL is a strong indicator that the patient has used marijuana. The metabolite of marijuana (THC-COOH) has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine >100 ng/mL indicates relatively recent use, probably within the past 7 days. Levels >500 ng/mL suggest chronic and recent use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

**Reference Values:**
Negative
Carcinoembryonic Antigen (CEA), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant liver disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carcinoembryonic antigen (CEA) is a glycoprotein that is shed from the surface of malignant cells. Measurement of CEA in ascitic fluid has been proposed as a helpful test in detecting
malignancy-related ascites given the limited sensitivity of cytology.

**Useful For:** An adjunct to cytology to differentiate between malignancy-related and benign causes of ascites formation

**Interpretation:** A peritoneal fluid carcinoembryonic antigen (CEA) concentration >6.0 ng/mL is suspicious but not diagnostic of malignancy-related ascites. This clinical decision limit cutoff yielded 48% sensitivity and 99% specificity in a study of 137 patients presenting with ascites. CEA concentrations were significantly higher in ascites caused by malignancies known to be associated with elevated serum CEA levels including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, ascites caused by other malignancies such as lymphoma, mesothelioma, leukemia, and melanoma and hepatocellular carcinoma, routinely had CEA concentrations <6.0 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CEA levels in serum.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Carcinoembryonic Antigen (CEA), Pleural Fluid**

**Clinical Information:** Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, often requiring cytological examination of the pleural fluid and imaging studies of the pleural tissue. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology and imaging findings. Carcinoembryonic antigen (CEA) is a glycoprotein produced during fetal development. Nonsmoking, healthy adults typically produce low to undetectable levels of CEA. Serum concentrations of CEA may be elevated in patients with certain malignancies that secrete CEA into circulation, including medullary thyroid carcinoma and breast, gastrointestinal tract, colorectal, liver, lung, ovarian, pancreatic, and prostate cancers. Pleural fluid concentrations of CEA have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CEA and elevate serum CEA concentrations, including lung, breast, ovarian, gastrointestinal, and colorectal cancers, typically also elevate CEA in pleural fluid. In contrast, malignancies that do not secrete CEA, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CEA in pleural fluid comparable to concentrations observed in non-malignant effusions. Elevated CEA concentrations in pleural fluid have also been reported with certain nonmalignant conditions, including liver cirrhosis, pancreatitis, complicated parapneumonic effusions and empyemas, and rarely with tuberculosis. CEA results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

**Useful For:** An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

**Interpretation:** A pleural fluid carcinoembryonic antigen (CEA) concentration of > or =3.5 ng/mL is suspicious but not diagnostic of a malignant source of the effusion. This cutoff yielded a sensitivity of 52%, specificity of 95%, and part per volume of 93% in a study of 200 patients presenting with effusion. CEA concentrations were significantly higher in effusions caused by CEA-secreting malignancies, including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, effusions caused by non-CEA-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CEA concentrations <3.5 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CEA-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

**Reference Values:**
An interpretive report will be provided.


### CEA

**Carcinoembryonic Antigen (CEA), Serum**

**Clinical Information:** Carcinoembryonic antigen (CEA) is a glycoprotein normally found in embryonic entodermal epithelium. Increased levels may be found in patients with primary colorectal cancer or other malignancies including medullary thyroid carcinoma and breast, gastrointestinal tract, liver, lung, ovarian, pancreatic, and prostatic cancers. Serial monitoring of CEA should begin prior to therapy to verify post therapy decrease in concentration and to establish a baseline for evaluating possible recurrence. Levels generally return to normal within 1 to 4 months after removal of cancerous tissue.

**Useful For:** Monitoring colorectal cancer and selected other cancers such as medullary thyroid carcinoma

**Interpretation:** Grossly elevated carcinoembryonic antigen (CEA) concentrations (>20 ng/mL) in a patient with compatible symptoms are strongly suggestive of the presence of cancer and also suggest metastasis. Most healthy subjects (97%) have values < or =3.0 ng/mL. After removal of a colorectal tumor, the serum CEA concentration should return to normal by 6 weeks, unless there is residual tumor. Increases in test values over time in a patient with a history of cancer suggest tumor recurrence.

**Reference Values:**
Non-smokers: < or =3.0 ng/mL
Some smokers may have elevated CEA, usually <5.0 ng/mL.
Serum markers are not specific for malignancy, and values may vary by method.


### CEASF

**Carcinoembryonic Antigen (CEA), Spinal Fluid**

**Clinical Information:** Carcinoembryonic antigen (CEA) normally is present in cerebrospinal fluid (CSF) in very low concentrations. Elevations in serum CEA can cause passive transfer to CSF. Tumors of the brain, especially metastatic tumors, can elevate CSF CEA.

**Useful For:** Detecting meningeal carcinomatosis, intradural or extradural infiltration, or brain parenchymal metastasis from adenocarcinoma or squamous-cell carcinoma

**Interpretation:** Increased values are seen in approximately 60% of patients with meningeal carcinomatosis.

**Reference Values:** <0.6 ng/mL
Tumor markers are not specific for malignancy, and values may vary by method.


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**Cardamom, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Cardiac Fibrinogen, Plasma**

**Clinical Information:** Elevated plasma fibrinogen is a risk factor for cardiovascular disease.(1) Fibrinogen contributes to cardiovascular disease risk through a variety of mechanisms. Plasma viscosity is
strongly influenced by fibrinogen concentrations. Fibrinogen is an acute-phase reactant indicative of chronic inflammatory status. Most importantly, fibrinogen and its enzymatic degradation product fibrin bind specifically to activated platelets to promote platelet aggregation and blood clotting. Carotid intimamedia thickness, a radiological measure of atherosclerosis, is significantly correlated with plasma fibrinogen concentrations. (2) Addition of plasma fibrinogen measurement to a prognostic model for cardiovascular disease that includes age, gender, tobacco use, blood pressure, history of diabetes, high density lipoprotein, and total cholesterol significantly improves 10-year risk classification. Fibrinogen assessment in patients at intermediate risk according to conventional biomarkers significantly improves classification. (3) Plasma fibrinogen concentrations can be significantly lowered by smoking cessation and increased physical activity. (4, 5)

**Useful For:** Evaluating risk of atherosclerosis and adverse events related to atherosclerotic disease

**Interpretation:** Elevated plasma fibrinogen confers increased risk of atherosclerosis, acute myocardial infarction, and stroke.

**Reference Values:**
- <340 mg/dL 1st quartile (low risk)
- 340-390 mg/dL 2nd quartile
- 391-450 mg/dL 3rd quartile
- >450 mg/dL 4th quartile (high risk)

**Clinical References:**

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**Cardiovascular or Cardiopulmonary Consultation, Autopsy**

**Clinical Information:** Difficult cardiovascular and cardiopulmonary abnormalities, including congenital anomalies, sometimes require the assistance of a cardiac pathologist. This evaluation is offered to provide the careful dissection and diagnostic experience that may be needed for unusual or rare cardiovascular or cardiopulmonary cases.

**Useful For:** Evaluation of congenital heart disease Evaluation of pulmonary hypertension Evaluation of complex ischemic or valvular heart disease Evaluation of cardiomyopathies Evaluation of sudden unexplained death Not for cases under litigation

**Interpretation:** This request will be processed as a consultation. Appropriate stain(s) will be performed and a diagnostic interpretation provided.

**Reference Values:**
Abnormalities will be compared to reported reference values.

**Clinical References:**

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**CVRMP**

Cardiovascular Risk Marker Panel, Serum

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: Cardiovascular disease is the number 1 cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually. Many of these events occur in individuals who have no prior symptoms. Standard risk factors, including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, predict only about 65% of individuals who will go on to have a cardiovascular event. Therefore, identification of patients with residual risk is important to target lifestyle and pharmaceutical intervention to those at higher risk of future events. Many additional risk markers have been identified for cardiovascular disease but few have emerged as independent risk markers. Two of these additional risk markers, high-sensitivity C-reactive protein (hsCRP) and lipoprotein (a) (Lp[a]), are clearly shown to be independently associated with increased risk of future cardiovascular events. Several recent guidelines have suggested that clinicians utilize hsCRP and Lp(a) in selected persons to augment risk classification, guide intensity of risk-reduction therapy and modulate clinical judgment when making therapeutic decision.(1-3) Prospective studies assessing these risk factors individually have determined them to be independently associated with increased risk for the development of ischemic events. Guidelines recommend measurement of additional risk markers in individuals who are at intermediate risk for developing cardiovascular disease, those with early atherosclerosis without explanation by abnormalities of traditional risk factors, and those with a strong family history of cardiovascular disease without the presence of traditional risk factors.

Useful For: Assessment for risk of developing cardiovascular disease, major adverse cardiovascular events, or ischemic cerebrovascular events

Interpretation: Specific interpretations are provided based on lipid results according to Mayo Clinic care process models. Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Medical Laboratories reports (see Reference Values). More aggressive treatment strategies may be pursued in patients determined to be at increased risk.

Reference Values:
Reference values apply to fasting specimens only.

Non-HDL CHOLESTEROL
2 to 17 years**
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

> or =18 years*
Desirable: <130 mg/dL
Above Desirable: 130-159 mg/dL
Borderline high: 160-189 mg/dL
High: 190-219 mg/dL
Very high: > or =220 mg/dL

LDL CHOLESTEROL
2 to 17 years**
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

> or =18 years*
Desirable: <100 mg/dL
Above Desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

HDL CHOLESTEROL
Males:
2 to 17 years**
Low: <40 mg/dL  
Borderline low: 40-45 mg/dL  
Acceptable: > 45 mg/dL  
> or =18 years*: > or =40 mg/dL

Females  
2 to 17 years**  
Low: <40 mg/dL  
Borderline low: 40-45 mg/dL  
Acceptable: > 45 mg/dL  
> or =18 years*: > or = 50 mg/dL

TOTAL CHOLESTEROL  
2 to 17 years**  
Acceptable: <170 mg/dL  
Borderline high: 170-199 mg/dL  
High: > or =200 mg/dL  
> or =18 years***  
Desirable: <200 mg/dL  
Borderline high: 200-239 mg/dL  
High: > or =240 mg/dL

TRIGLYCERIDES  
2 to 9 years**  
Acceptable: <75 mg/dL  
Borderline high: 75-99 mg/dL  
High: > or =100 mg/dL  
10 to 17 years**  
Acceptable: <90 mg/dL  
Borderline high: 90-129 mg/dL  
High: > or =130 mg/dL  
> or =18 years*  
Normal: <150 mg/dL  
Borderline high: 150-199 mg/dL  
High: 200-499 mg/dL  
Very high: > or =500 mg/dL

LIPOPROTEIN (a)  
< or =30 mg/dL  
Values >30 mg/dL may suggest increased risk of coronary heart disease.

C-REACTIVE PROTEIN HIGH SENSITIVITY*  
Lower risk: <2.0 mg/L  
Higher risk: >=2.0 mg/L  
Acute inflammation: >10.0 mg/L

*National Lipid Association 2014  
**Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents  
***National Cholesterol Education Program (NCEP)

Carmine Dye/Red Dye Cochineal (Dactylopius coccus) IgE (Red # 4)

**Interpretation:** Class IgE (kU/L)
- Comment 0 <0.10 Negative
- 0.10-0.34 Equivocal
- 0.35-0.69 Low Positive
- 0.70-3.4 Moderate Positive
- 3.5-17.4 High Positive
- 17.5-49.9 Very High Positive
- 50.0-99.9 Very High Positive
- > or = 100 Very High Positive

**Reference Values:**
<0.35 kU/L

Carnitine Palmitoyltransferase II Deficiency, Full Gene Analysis

**Clinical Information:** Carnitine palmitoyltransferase II (CPT II) deficiency is an autosomal recessive disorder of long-chain fatty-acid oxidation. There are 3 distinct clinical phenotypes: a lethal neonatal form, an early-onset infantile form, and a late-onset adult myopathic form. The lethal neonatal and early-onset infantile forms are characterized by liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia, peripheral myopathy and early death. The adult-onset myopathic form is the most common type and is characterized by exercise-induced muscle pain and weakness and may be associated with myoglobinuria. Males are more likely to be affected with the myopathic form than females. Initial screening can be done with plasma acylcarnitines. Definitive diagnosis can be made by detection of reduced CPT enzyme activity. Mutations in the CPT2 gene are responsible for CPT II deficiency and sequencing of this gene is recommended after positive biochemical analysis.

**Useful For:** Confirmation of diagnosis of carnitine palmitoyltransferase II deficiency Carrier screening in cases where there is a family history of carnitine palmitoyltransferase II deficiency, but disease-causing mutations have not been identified in an affected individual.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Carnitine, Plasma

**Clinical Information:** Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Buffering the ratio of free CoA to esterified CoA...
Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, tissue, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter disorders, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Individually, the incidence of these disorders varies from <1 in 10,000 to >1 in 1,000,000 live births. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions which could cause an abnormal carnitine level are neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Carnitine (TC) Range*</th>
<th>Free Carnitine (FC) Range*</th>
<th>Acylcarnitine (AC) Range*</th>
<th>AC/FC Ratio Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 day</td>
<td>23-68</td>
<td>12-36</td>
<td>7-37</td>
<td>0.4-1.7</td>
</tr>
<tr>
<td>2-7 days</td>
<td>17-41</td>
<td>10-21</td>
<td>3-24</td>
<td>0.2-1.4</td>
</tr>
<tr>
<td>8-31 days</td>
<td>19-59</td>
<td>12-46</td>
<td>4-15</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>32 days-12 months</td>
<td>38-68</td>
<td>27-49</td>
<td>7-19</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>13 months-6 years</td>
<td>35-84</td>
<td>24-63</td>
<td>4-28</td>
<td>0.1-0.8</td>
</tr>
<tr>
<td>7-10 years</td>
<td>28-83</td>
<td>22-66</td>
<td>3-32</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>11-17 years</td>
<td>34-77</td>
<td>22-65</td>
<td>4-29</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>34-78</td>
<td>25-54</td>
<td>5-30</td>
<td>0.1-0.8</td>
</tr>
</tbody>
</table>


**Clinical References:**

primary functions: Importing long-chain fatty acids into the mitochondria - Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Buffering the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, tissue, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter disorders, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Individually, the incidence of these disorders varies from <1 in 10,000 to >1 in 1,000,000 live births. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions which could cause an abnormal carnitine level are neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Carnitine (TC)</th>
<th>Free Carnitine (FC)</th>
<th>Acylcarnitine (AC)</th>
<th>AC/FC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 day</td>
<td>Range*</td>
<td>Range*</td>
<td>Range*</td>
<td>0.4-1.7</td>
</tr>
<tr>
<td>2-7 days</td>
<td>23-68</td>
<td>12-36</td>
<td>7-37</td>
<td>0.2-1.4</td>
</tr>
<tr>
<td>8-31 days</td>
<td>19-59</td>
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**Clinical References:**

Carnitine, Urine

Clinical Information: Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally occurring short-chain acyl-CoA groups from the mitochondria -Buffering the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, tissue, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic aciđemias and fatty acid oxidation disorders. In the latter, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Individually, the incidence of these disorders varies from <1 in 10,000 to >1 in 1,000,000 live births. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions which could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

Useful For: Evaluation of patients with a clinical suspicion of a wide range of conditions including organic aciđemias and fatty acid oxidation disorders Monitoring carnitine treatment

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
FREE
77-214 nmol/mg of creatinine

TOTAL
180-412 nmol/mg of creatinine

RATIO
Acyl to free: 0.7-3.4


CACTZ 35379

Carnitine-Acylcarnitine Translocase Deficiency, Full Gene Analysis

Clinical Information: Carnitine-acylcarnitine translocase (CACT) deficiency is a rare autosomal recessive disorder of fatty acid oxidation. The disease typically presents in the neonatal period with severe hypoketotic hypoglycemia, hyperammonemia, cardiac abnormalities, hepatic dysfunction, skeletal muscle weakness, encephalopathy, and early death. However, presentations at a later age with a milder phenotype have also been reported. Initial screening can be done with plasma acylcarnitines. Definitive diagnosis can be made by detection of reduced CACT enzyme activity. Mutations in the SLC25A20 gene are responsible for CACT deficiency, and sequencing of this gene is recommended after positive biochemical analysis.
**Useful For:** Confirmation of diagnosis of carnitine-acylcarnitine translocase (CACT) deficiency

Carrier screening in cases where there is a family history of CACT deficiency, but disease-causing mutations have not been identified in an affected individual

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


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**CAROB 82368 Carob, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
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<td>4</td>
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<tr>
<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Carrot IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Carrot, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Casein IgG

**Interpretation:** mcg/mL of IgG 
- Lower Limit of Quantitation: 2.0 
- Upper Limit of Quantitation: 200

**Reference Values:**
- < 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Casein, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Class IgE kU/L</th>
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<td>6 &gt; or =100</td>
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</tbody>
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Reference values apply to all ages.

### Cashew IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

- < 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Cashew, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

CASPZ 37439

CASP Gene, Full Gene Analysis

Clinical Information: The extracellular G-protein-coupled calcium-sensing receptor (CASP) is an essential component of calcium homeostasis. CASP is expressed at particularly high levels in the parathyroid glands and kidneys. It forms stable homodimeric cell-membrane complexes, which signal upon binding of extracellular calcium ions (Ca++)). In the parathyroid glands, this results in downregulation of gene expression of the main short-term regulator of calcium homeostasis, parathyroid hormone (PTH), as well as diminished secretion of already synthesized PTH. At the same time, renal calcium excretion is upregulated and sodium chloride excretion is downregulated. Ca(++) binding to CASP is highly cooperative within the physiological Ca(++) concentration range, leading to a steep dose-response curve, which results in tight control of serum calcium levels. To date, over 100 different alterations in the CASP gene have been described. Many of these cause diseases of abnormal serum calcium regulation. Inactivating mutations result in undersensing of Ca(++) concentrations and consequent PTH overproduction and secretion. This leads to either familial hypocalciuric hypercalcemia (FHH) or neonatal severe primary hyperparathyroidism (NSPHT), depending on the severity of the functional impairment. Except for a very small percentage of cases with no apparent CASP mutations, FHH is due to heterozygous inactivating CASP mutations. Serum calcium levels are mildly-to-moderately elevated. PTH is within the reference range or modestly elevated, phosphate is normal or slightly low, and urinary calcium excretion is low for the degree of hypercalcemia. Unlike patients with primary hyperparathyroidism (PHT), which can be difficult to distinguish from FHH, the majority of FHH patients do not seem to suffer any adverse long-term effects from hypercalcemia and elevated PTH levels. They should, therefore, generally not undergo parathyroidectomy. NSPHT is usually due to homozygous or compound heterozygous inactivating CASP mutations, but can occasionally be caused by dominant-negative heterozygous mutations. The condition presents at birth, or shortly thereafter, with severe hypercalcemia requiring urgent parathyroidectomy. Activating mutations lead to oversensing of Ca(++)+, resulting in suppression of PTH secretion and consequently hypoparathyroidism. All activating mutations described are functionally dominant and disease inheritance is therefore autosomal dominant. However, sporadic cases also occur. Autosomal dominant hypoparathyroidism caused by CASP mutations may account for many cases of idiopathic hypoparathyroidism. Disease severity depends on the degree of gain of function, spanning the spectrum from mild hypoparathyroidism, which is diagnosed incidentally, to severe and early onset disease. In addition, while the majority of patients suffer only from hypoparathyroidism, a small subgroup with extreme gain of function mutations suffer from concomitant inhibition of renal sodium chloride transport. These individuals may present with additional symptoms of hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypomagnesemia, consistent with type V Bartter syndrome.

Useful For: Establishing a diagnosis of familial hypocalciuric hypercalcemia As part of the workup of some patients with primary hyperparathyroidism Establishing a diagnosis of neonatal severe primary hyperparathyroidism Establishing a diagnosis of autosomal dominant hypoparathyroidism As part of the workup of idiopathic hypoparathyroidism As part of the workup of patients with Bartter syndrome

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided

Castor Bean, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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</tr>
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</table>

Reference values apply to all ages.
Cat Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Catechol-O-Methyltransferase (COMT) Genotype, Saliva

Clinical Information: Catechol-O-methyltransferase (COMT) is involved in phase II (conjugative) metabolism of catecholamines and catechol drugs, such as dopamine, as well as the catechol-estrogens. COMT transfers a donor methyl-group from S-adenosylmethionine to acceptor hydroxy groups on catechol structures (aromatic ring structures with vicinal hydroxy-groups).(1) Bioactive catecholamine metabolites are metabolized by COMT in conjunction with monoamine oxidase (MAO): -Norepinephrine is methylated by COMT-forming normetanephrine. -Epinephrine is methylated by COMT-forming metanephrine. -Dopamine is converted to homovanillic acid through the combined action of MAO and...
COMT. Parkinsonism patients receiving levodopa (L-dopa) therapy are frequently also prescribed a COMT inhibitor to minimize metabolism of L-dopa by COMT, thereby prolonging L-dopa action. COMT is also involved in the inactivation of estrogens. Estradiol can be hydroxylated forming the catechol estrogens 2-hydroxyestradiol and 4-hydroxyestradiol.(2) These hydroxylated estrogens are methylated by COMT, forming the corresponding methoxyestra diols. Several studies have indicated the increased risk of breast cancer due to low-activity COMT.(3) The gene encoding COMT is transcribed from alternative promoters to produce 2 forms of the enzyme, a soluble short form of the enzyme and a membrane-bound long form. Variants in the COMT gene are therefore designated in the literature by the position of the amino acid change in both the short and long form of the enzyme. A single nucleotide polymorphism in exon 4 of the gene produces an amino acid change from valine to methionine (Val108/158Met). This polymorphism, COMT*2, reduces the maximum activity of the variant enzyme by 25% and also results in significantly less immunoreactive COMT protein, resulting in a 3- to 4-fold decrease in activity compared to wild type COMT*1. The COMT*2 polymorphism has been linked to prefrontal cortex cognitive response to antipsychotic medications. Schizophrenia patients homozygous for the *2 polymorphism displayed improved cognition following drug treatment. Patients homozygous for *1 did not have improved cognition following treatment.(6) A second polymorphism has been identified in exon 4 that results in a threonine substitution for alanine (Ala52/102Thr). This polymorphism, COMT*3, does not reduce enzyme activity and is predicted to be a normally functioning allele.

Useful For: Early identification of patients who may show cognitive improvement with treatment for schizophrenia; this is associated with the COMT*2/ COMT*2 genotype Investigation of inhibitor dosing for decreasing L-dopa metabolism Research use for assessing estrogen metabolism Genotyping patients who prefer not to have venipuncture done

Interpretation: An interpretive report will be provided. The normal genotype (wild type) for COMT is *1/*1. COMT*2 (Val108/158Met) leads to a reduced activity allele. COMT*3 (Ala52/102Thr) is a normal activity allele. The following information outlines the relationship between polymorphisms detected in this assay and the effect on the activity of the enzyme produced by that allele: COMT Allele Amino Acid Change Effect on Enzyme Activity/Metabolism *1 None (wild-type) Normal/Extensive *2 Val108/158Met Reduced/Poor *3 Ala52/102Thr Normal/Extensive

Reference Values: An interpretive report will be provided.


**Catechol-O-Methyltransferase Genotype**

Clinical Information: Catechol-O-methyltransferase (COMT) is involved in phase II (conjugative) metabolism of catecholamines and catechol drugs, such as dopamine, as well as the catechol-estrogens. COMT transfers a donor methyl-group from S-adenosylmethionine to acceptor hydroxy groups on catechol structures (aromatic ring structures with vicinal hydroxy-groups).(1) Bioactive catecholamine metabolites are metabolized by COMT in conjunction with monoamine oxidase (MAO): - Norepinephrine is methylated by COMT forming normetanephrine. - Epinephrine is methylated by COMT forming metanephrine. - Dopamine is converted to homovanillic acid through the combined action of MAO and COMT. Parkinsonism patients receiving levodopa (L-DOPA) therapy are frequently also prescribed a
COMT inhibitor to minimize metabolism of L-DOPA by COMT, thereby prolonging L-DOPA action. COMT is also involved in the inactivation of estrogens. Estradiol can be hydroxylated forming the catechol estrogens 2-hydroxyestradiol and 4-hydroxyestradiol. These hydroxylated estradiols are methylated by COMT, forming the corresponding methoxyestradiols. Several studies have indicated the increased risk of breast cancer due to low activity COMT. The gene encoding COMT is transcribed from alternative promoters to produce 2 forms of the enzyme, a soluble short form of the enzyme and a membrane-bound long form. Variants in the COMT gene are therefore designated in the literature by the position of the amino acid change in both the short and long form of the enzyme. A single nucleotide polymorphism in exon 4 of the gene produces an amino acid change from valine to methionine (Val108/158Met). This polymorphism, COMT*2, reduces the maximum activity of the variant enzyme by 25% and also results in significantly less immunoreactive COMT protein, resulting in a 3-fold to 4-fold decrease in activity compared to wild type COMT*1. The COMT*2 polymorphism has been linked to prefrontal cortex cognitive response to antipsychotic medications. Schizophrenia patients homozygous for the *2 polymorphism displayed improved cognition following drug treatment. Patients homozygous for *1 did not have improved cognition following treatment. A second polymorphism has been identified in exon 4 that results in a threonine substitution for alanine (Ala52/102Thr). This polymorphism, COMT*3, does not reduce enzyme activity and is predicted to be a normally functioning allele.

**Useful For:** Early identification of patients who may show cognitive improvement with treatment for schizophrenia; this is associated with the COMT*2/COMT*2 genotype. Investigation of inhibitor dosing for decreasing L-DOPA metabolism. Research use for assessing estrogen metabolism.

**Interpretation:** An interpretive report will be provided. The normal genotype (wild-type) for COMT is *1/*1. COMT*2 (Val108/158Met) leads to a reduced activity allele. COMT*3 (Ala52/102Thr) is a normal activity allele. The following information outlines the relationship between polymorphisms detected in this assay and the effect on the activity of the enzyme produced by that allele: COMT Allele Amino Acid Change Effect on Enzyme Activity/Metabolism *1 None (wild-type) Normal/Extensive *2 Val108/158Met Reduced/Poor *3 Ala52/102Thr Normal/Extensive

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


**CATU 9276 Catecholamine Fractionation, Free, 24 Hour, Urine**

**Clinical Information:** The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and play crucial roles in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but also differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. They are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, and other stimuli.
emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma, a potentially curable tumor of catecholamine producing cells of the adrenal medulla, or less commonly of sympathetic ganglia (paraganglioma), urine catecholamine levels may be elevated. This results in episodic or sustained hypertension and often in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea ("spells"). Elevations of the urine levels of 1 or several of the catecholamines also may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines, or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

**Useful For:** An auxiliary test to fractionated plasma and urine metanephrine measurements in the diagnosis of pheochromocytoma and paraganglioma An auxiliary test to urine vanillylmandelic acid and homovanillic acid determination in the diagnosis and follow-up of patients with neuroblastoma and related tumors

**Interpretation:** Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma. PMET / Metanephrines, Fractionated, Free, Plasma (the most sensitive assay) and/or METAF / Metanephrines, Fractionated, 24 Hour, Urine (almost as sensitive and highly specific) are the recommended first-line laboratory tests for pheochromocytoma. However, urine catecholamine measurements can still be useful in patients whose plasma metanephrines or urine metanephrines measurements do not completely exclude the diagnosis. In such cases, urine catecholamine specimens have an 86% diagnostic sensitivity when cut-offs of >80 mg/24 hour for norepinephrine and >20 mg/24 hour for epinephrine are employed. Unfortunately, the specificity of these cut-off levels for separating tumor patients from other patients with similar symptoms is only 88%. When more specific (98%) decision levels of >170 mg/24 hours for norepinephrine or >35 mg/24 hours for epinephrine are used, the assayâ€™s sensitivity falls to about 77%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements on spot urine or 24-hour urine are the mainstay of biochemical diagnosis and follow-up of neuroblastoma; 1 or more of these tests may be elevated.

**Reference Values:**

### Norepinephrine

- <1 year: <11 mcg/24 hours
- 1 year: 1-17 mcg/24 hours
- 2-3 years: 4-29 mcg/24 hours
- 4-6 years: 8-45 mcg/24 hours
- 7-9 years: 13-65 mcg/24 hours
- > or =10 years: 15-80 mcg/24 hours

### Epinephrine

- <1 year: <2.6 mcg/24 hours
- 1 year: <3.6 mcg/24 hours
- 2-3 years: <6.1 mcg/24 hours
- 4-9 years: 0.2-10.0 mcg/24 hours
- 10-15 years: 0.5-20.0 mcg/24 hours
- > or =16 years: <21 mcg/24 hours

### Dopamine

- <1 year: <86 mcg/24 hours
- 1 year: 10-140 mcg/24 hours
- 2-3 years: 40-260 mcg/24 hours
- > or =4 years: 65-400 mcg/24 hours

Catecholamine Fractionation, Free, Plasma

Clinical Information: The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and also play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap, but also differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. The catecholamines are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine-producing cells of the adrenal medulla), or less commonly of sympathetic ganglia (paraganglioma), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of 1 or several of the catecholamines may also be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction or failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

Useful For: Diagnosis of pheochromocytoma and paraganglioma, as an auxiliary test to fractionated plasma and urine metanephrine measurements (plasma metanephrine is the preferred test for this diagnosis) Diagnosis and follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction or failure or autonomic neuropathy

Interpretation: Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated, but only secreted during a “spell.” By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can still be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if drawn during a “spell,” have a 90% to 95% diagnostic sensitivity when cutoffs of >750 pg/mL for norepinephrine and >110 pg/mL for epinephrine are employed. A lower value during a “spell,” particularly when plasma or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not good for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2,000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay's sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements on spot urine or 24-hour urine are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be
observed in these tumors. Diagnosis of Autonomic Dysfunction or Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction or failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels, or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

**Reference Values:**

**NOREPINEPHRINE**
- Supine: 70-750 pg/mL
- Standing: 200-1,700 pg/mL

**EPINEPHRINE**
- Supine: < or =111 pg/mL
- Standing: < or =141 pg/mL

**DOPAMINE**
- <30 pg/mL (no postural change)


**FCATE 57554**

**Catfish (Siluriformes spp) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**
- <0.35 kU/L

**FCLPS 91193**

**Cathartic Laxatives Profile, Stool**

**Reference Values:**

Reporting limit determined each analysis

- Magnesium (mg/g)

Mgnumine concentrations in stool water above the normal levels of 0.7-1.2 mg/mL have been indicative of surreptitious abuse of magnesium containing laxatives.

NMS Labs Calculated Normal: approximately 0.5-10 mg/g (Based on the reported range of magnesium eliminated per day in stool and the range of stool mass per day in adults). Not for clinical diagnostic purposes.
Phosphorus (mg/g)

Phosphorus concentration in stool water averaged 1.8 +/- 0.3 mg/mL (ranged from 0.3-4.2 mg/mL) following administration of 105 mmol of sodium phosphate.

NMS Labs calculated normal: approximately 1.4-22 mg/g (Based on the reported range of phosphorus eliminated per day in stool and the range of stool mass per day in adults).

Not for clinical diagnostic purposes.

FCAFG 57680

Cauliflower IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

CALFL 82617

Cauliflower, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>
CBC

Red Blood Cell Count (RBC)

<table>
<thead>
<tr>
<th>Age</th>
<th>Male Range</th>
<th>Female Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>3.90-5.50 x 10^{12}/L</td>
<td>3.90-5.50 x 10^{12}/L</td>
</tr>
<tr>
<td>1-7 days</td>
<td>3.90-6.00 x 10^{12}/L</td>
<td>3.90-6.00 x 10^{12}/L</td>
</tr>
<tr>
<td>8-14 days</td>
<td>3.60-6.00 x 10^{12}/L</td>
<td>3.60-6.00 x 10^{12}/L</td>
</tr>
<tr>
<td>15 days-1 month</td>
<td>3.00-5.50 x 10^{12}/L</td>
<td>3.00-5.50 x 10^{12}/L</td>
</tr>
<tr>
<td>2-5 months</td>
<td>3.10-4.50 x 10^{12}/L</td>
<td>3.10-4.50 x 10^{12}/L</td>
</tr>
<tr>
<td>6 months-1 year</td>
<td>3.70-6.00 x 10^{12}/L</td>
<td>3.70-6.00 x 10^{12}/L</td>
</tr>
<tr>
<td>2 years</td>
<td>4.10-5.10 x 10^{12}/L</td>
<td>4.10-5.10 x 10^{12}/L</td>
</tr>
<tr>
<td>3-5 years</td>
<td>4.10-5.30 x 10^{12}/L</td>
<td>4.10-5.30 x 10^{12}/L</td>
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<tr>
<td>6-11 years</td>
<td>4.20-5.10 x 10^{12}/L</td>
<td>4.20-5.10 x 10^{12}/L</td>
</tr>
<tr>
<td>12-15 years</td>
<td>4.40-5.50 x 10^{12}/L</td>
<td>4.40-5.50 x 10^{12}/L</td>
</tr>
<tr>
<td>Adults</td>
<td>4.32-5.72 x 10^{12}/L</td>
<td>3.90-5.03 x 10^{12}/L</td>
</tr>
</tbody>
</table>

HEMOGLOBIN
Males:
Birth-7 days: 13.5-22.0 g/dL
8-14 days: 12.5-21.0 g/dL
15 days-1 month: 10.0-20.0 g/dL
2-5 months: 10.0-14.0 g/dL
6 months-1 year: 10.5-13.5 g/dL
2 years: 11.0-14.0 g/dL
3-5 years: 11.0-14.5 g/dL
6-11 years: 12.0-14.0 g/dL
12-15 years: 12.8-16.0 g/dL
Adults: 13.5-17.5 g/dL
Females:
Birth-7 days: 13.5-22.0 g/dL
8-14 days: 12.5-21.0 g/dL
15 days-1 month: 10.0-20.0 g/dL
2-5 months: 10.0-14.0 g/dL
6 months-1 year: 10.5-13.5 g/dL
2 years: 11.0-14.0 g/dL
3-5 years: 11.8-14.7 g/dL
6-11 years: 12.0-14.5 g/dL
12-15 years: 12.2-14.8 g/dL
Adults: 12.0-15.5 g/dL

HEMATOCRIT
Males:
Birth-7 days: 42.0-60.0% 
8-14 days: 39.0-60.0% 
15 days-1 month: 31.0-55.0% 
2-5 months: 28.0-42.0% 
6 months-1 year: 33.0-40.0% 
2 years: 33.0-42.0% 
3-5 years: 33.0-43.0% 
6-11 years: 35.8-42.4% 
12-15 years: 37.3-47.3% 
Adults: 38.8-50.0%
Females:
Birth-7 days: 42.0-60.0% 
8-14 days: 39.0-60.0% 
15 days-1 month: 31.0-55.0% 
2-5 months: 28.0-42.0% 
6 months-1 year: 33.0-40.0% 
2 years: 33.0-42.0% 
3-5 years: 35.0-44.0% 
6-11 years: 35.7-43.0% 
12-15 years: 36.3-43.4% 
Adults: 34.9-44.5%

MEAN CORPUSCULAR VOLUME (MCV)
Males:
Birth: 98.0-120.0 fl
1-7 days: 88.0-120.0 fl
8-14 days: 86.0-120.0 fl
15 days-1 month: 85.0-110.0 fl
2-5 months: 77.0-110.0 fl
6 months-5 years: 74.0-89.0 fl
6-11 years: 76.5-90.6 fl
12-15 years: 81.4-91.9 fl

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### Adult Reference Values

**Adults:** 81.2-95.1 fL  
**Females:**  
**Birth:** 98.0-120.0 fL  
1-7 days: 88.0-120.0 fL  
8-14 days: 86.0-120.0 fL  
15 days-1 month: 85.0-110.0 fL  
2-5 months: 77.0-110.0 fL  
6 months-5 years: 74.0-89.0 fL  
6-11 years: 78.5-90.4 fL  
12-15 years: 79.9-92.3 fL  
**Adults:** 81.6-98.3 fL

### Red Cell Distribution Width (RDW)

**Males:**  
<2 years: not established  
2 years: 12.0-14.5%  
3-5 years: 12.0-14.0%  
6-11 years: 12.0-14.0%  
12-15 years: 11.6-13.8%  
**Adults:** 11.8-15.6%  
**Females:**  
<2 years: not established  
2 years: 12.0-14.5%  
3-5 years: 12.0-14.0%  
6-11 years: 11.6-13.4%  
12-15 years: 11.2-13.5%  
**Adults:** 11.9-15.5%

### White Blood Cell Count (WBC)

**Males:**  
Birth: 9.0-30.0 x 10^9/L  
1-7 days: 9.4-34.0 x 10^9/L  
8-14 days: 5.0-21.0 x 10^9/L  
15 days-1 month: 5.0-20.0 x 10^9/L  
2-5 months: 5.0-15.0 x 10^9/L  
6 months-1 year: 6.0-11.0 x 10^9/L  
2 years: 5.0-12.0 x 10^9/L  
3-5 years: 4.0-12.0 x 10^9/L  
6-11 years: 3.4-9.5 x 10^9/L  
12-15 years: 3.6-9.1 x 10^9/L  
**Adults:** 3.5-10.5 x 10^9/L  
**Females:**  
Birth: 9.0-30.0 x 10^9/L  
1-7 days: 9.4-34.0 x 10^9/L  
8-14 days: 5.0-21.0 x 10^9/L  
15 days-1 month: 5.0-20.0 x 10^9/L  
2-5 months: 5.0-15.0 x 10^9/L  
6 months-1 year: 6.0-11.0 x 10^9/L  
2 years: 5.0-12.0 x 10^9/L  
3-5 years: 4.0-12.0 x 10^9/L  
6-11 years: 3.4-10.8 x 10^9/L  
12-15 years: 4.1-8.9 x 10^9/L  
**Adults:** 3.5-10.5 x 10^9/L

### Platelets

- **Birth-5 months:** 150-350 x 10^9/L  
- **> or =6 months:** 150-450 x 10^9/L

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Page 414
NEUTROPHILS
Birth: 6.00-26.00 x 10^9/L
1-7 days: 1.50-10.00 x 10^9/L
8-14 days: 1.00-9.50 x 10^9/L
15 days-1 month: 1.00-9.00 x 10^9/L
2-5 months: 1.00-8.50 x 10^9/L
6 months-5 years: 1.50-8.50 x 10^9/L
6-11 years: 1.50-8.50 x 10^9/L
12-15 years: 1.80-8.00 x 10^9/L
Adults: 1.70-7.00 x 10^9/L

LYMPHOCYTES
Birth: 2.00-11.00 x 10^9/L
1-14 days: 2.00-17.00 x 10^9/L
15 days-1 month: 2.50-16.50 x 10^9/L
2-5 months: 4.00-13.50 x 10^9/L
6 months-11 months: 4.00-10.50 x 10^9/L
1-5 years: 1.50-7.00 x 10^9/L
6-11 years: 1.50-6.50 x 10^9/L
12-15 years: 1.20-5.20 x 10^9/L
Adults: 0.90-2.90 x 10^9/L

MONOCYTES
Birth-14 days: 0.40-1.80 x 10^9/L
15 days-11 months: 0.05-1.10 x 10^9/L
1-15 years: 0.00-0.80 x 10^9/L
Adults: 0.30-0.90 x 10^9/L

EOSINOPHILS
Birth-5 months: 0.02-0.85 x 10^9/L
6 months-11 months: 0.05-0.70 x 10^9/L
1-5 years: 0.00-0.65 x 10^9/L
6-15 years: 0.00-0.50 x 10^9/L
Adults: 0.05-0.50 x 10^9/L

BASOPHILS
Birth-5 months: 0.00-0.60 x 10^9/L
6 months-15 years: 0.00-0.20 x 10^9/L
> or =16 years: 0.00-0.30 x 10^9/L

Clinical References:

CD20B
CD20 on B Cells
Clinical Information: CD20 is a protein that is expressed on the surface of B cells, starting at the pre-B cell stage and also on mature B cells in the bone marrow and in the periphery. CD20 is not expressed on hematopoietic stem cells, pro-B cells, or normal plasma cells. (1) Plasmablasts and stimulated plasma cells may express CD20. (2) CD20 is generally coexpressed on B cells with CD19, another B-cell differentiation marker. CD20 appears to play a role in B-cell development, differentiation, B-cell receptor (BCR) signaling, and cell-cycle initiation events. (3) CD20 is not shed from the surface of B cells and does not internalize on binding with anti-CD20 antibody, nor is it typically present as a
soluble free antigen in circulation. Certain primary humoral immunodeficiencies, such as X-linked agammaglobulinemia and autosomal recessive agammaglobulinemia, are characterized by a complete absence or profound reduction of peripheral B cells, expressing both CD20 and CD19 (another B-cell differentiation marker). Mutations in the CD19 gene have been shown to be associated with a primary humoral immunodeficiency, sometimes classified as common variable immunodeficiency (CVID). This defect accounts for <1% to 2% of CVID patients and appears to be inherited as an autosomal recessive defect. Since these patients have normal numbers of B cells with absent CD19 expression on the cell surface, CD20 can be used as a marker to help identify these patients. A contrasting situation exists for patients receiving rituximab, ofatumumab, and other anti-CD20 monoclonal antibodies that are used to treat certain cancers, autoimmune diseases, or for B-cell depletion to prevent humoral rejection in positive crossmatch renal transplantation. These agents block available CD20-binding sites and, therefore, the antibody used for this flow cytometric assay cannot recognize the CD20 molecule on B cells. The concomitant use of the CD19 marker provides information on the extent of B-cell depletion when using this particular treatment strategy. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:**
- Evaluation of CD19 deficiency in patients with a suspected CD19 deficiency (humoral immunodeficiency)
- Confirming complete absence of B cells in suspected primary humoral immunodeficiencies using both CD19 and CD20 markers
- To assess therapeutic B-cell depletion quantitatively (absolute counts of cells/mcL) in any clinical context, including malignancies, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and membranous glomerulonephritis among others, and treatment or prevention of acute humoral rejection in positive crossmatch renal transplant recipients. This test is not useful for the following applications, instead TAE / Therapeutic Antibody by Flow Cytometry should be ordered in the contexts described below:
  - Assessing whether malignant (and nonmalignant) B cells express the target molecule (CD20) of interest in the context of initiating therapeutic monoclonal anti-CD20 antibody therapy (rituximab, ofatumumab, and tositumomab) for any of the hematological malignancies, or in other clinical contexts, such as autoimmunity.

**Interpretation:**
The presence of CD20+ B cells with corresponding absence of CD19 staining in individuals not receiving anti-CD20 monoclonal antibody treatment or with clinical features of variable primary humoral immunodeficiency may suggest an underlying CD19 deficiency, which should be further evaluated. Absence of both CD20 and CD19 markers on B cells in blood from individuals not on anti-CD20 monoclonal antibody treatment is consistent with complete mature and immature peripheral B-cell depletion, which may be due to an underlying primary immunodeficiency. Patients receiving B-cell depleting therapy with anti-CD20 antibodies can show unusual populations of B cells on reconstitution that express either CD19 or CD20 due to a phenomenon known as trogocytosis.

**Reference Values:**

- **%CD19 B CELLS**
  - > or =19 years: 4.6-22.1%

- **CD19 ABSOLUTE**
  - > or =19 years: 56.6-417.4 cells/mcL

- **%CD20 B CELLS**
  - > or =19 years: 5.0-22.3%

- **CD20 ABSOLUTE**
  - > or =19 years: 74.4-441.1 cells/mcL
CD45 ABSOLUTE
18-55 years: 0.99-3.15 thou/mcL
>55 years: 1.00-3.33 thou/mcL


CD4 Count for Immune Monitoring, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/ml) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of one or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 co-receptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T-lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

Useful For: Serial monitoring of CD4 T cell count in HIV-positive patients Useful for follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined
immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized. Assessment of T-cell immune reconstitution post hematopoietic cell transplantation. Early screening of gross quantitative anomalies in T cells in infection or malignancies.

**Interpretation:** HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count. (7,8) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with CD4 count <200 cells/mL.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

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**CD4 Count for Monitoring, New York, Blood**

**Clinical Information:** Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan T-cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon. (1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. (2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. (2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening (5) and during summer compared to winter. (6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe...
combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

**Useful For:** Serial monitoring of CD4 T-cell count in HIV-positive patients. Follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized. Assessment of T-cell immune reconstitution post hematopoietic cell transplantation. Early screening of gross quantitative anomalies in T cells in infection or malignancies.

**Interpretation:** HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count. (7,8) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with CD4 count <200 cells/mL.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**CD4 T-Cell Recent Thymic Emigrants (RTE) Clinical Information:** Naive T-cells are generated in the thymus and exported to peripheral blood to form the peripheral T-cell repertoire. There is a decrease in naive T cells derived from the thymus with age due to age-related decline in thymic output. Recent thymic emigrants (RTEs) typically refers to those populations of naive T cells that have not diluted their TREC copies (T-cell receptor excision circles) by homeostatic or antigen-driven cell division. Naive T cells can be long-lived in the periphery and postpuberty, and in adults, peripheral T-cell homeostasis is maintained by a balance of thymic output and peripheral T-cell expansion and this proportion changes with age. In infants and prepubertal children, the T-cell repertoire is largely maintained by thymic-derived naive T cells. RTEs express TREC indicative of naive T cells derived from the thymus.(1) In the CD4 T-cell compartment it has been shown that naive CD45RA+ T cells coexpressing CD31 had a higher frequency of TREC compared to T cells lacking CD31. (2) The higher proportion of TREC+ naive T cells indicate a more recent thymic ontogeny since TREC can be diluted by cell division (since they are extrachromosomal). It has been shown that CD31+CD4+ T cells continue to possess a relatively higher proportion of TREC despite an age-related 10-fold reduction after the neonatal period. (3) CD4 RTEs (CD31+CD4+CD45RA+) have longer telomeres and higher telomerase activity, which, along with the increased frequency of TREC positivity suggests a population of T cells with low replicative history. (3) The same study has also shown that CD31+ CD4+ T cells are an appropriate cell population to evaluate thymic reconstitution in lymphopenic children post hematopoietic cell transplant. (3) A Mayo study (unpublished) shows that the CD31 marker...
correlates with TREC-enriched T cells across the spectrum of age and correlates with thymic recovery in adults after autologous hematopoietic cell transplantation. CD31+ CD4 RTEs have also been used to evaluate T-cell homeostatic anomalies in patients with relapsing-remitting multiple sclerosis. For patients with DiGeorge syndrome (DGS)--a cellular immunodeficiency associated with other congenital problems including cardiac defects, facial dysmorphism, hypoparathyroidism, and secondary hypocalcemia, and chromosome 22q11.2 deletion (in a significant proportion of patients)--measurement of thymic function provides valuable information on the functional phenotype, ie, complete DGS (associated with thymic aplasia in a minority of patients) or partial DGS (generally well-preserved thymic function seen the in the majority of patients). Thymus transplants have been performed in patients with complete DGS, but are typically not required in partial DGS. There can be change in peripheral T-cell counts in DGS patients with age.

**Useful For:** Evaluating thymic reconstitution in patients following hematopoietic cell transplantation, chemotherapy, immunomodulatory therapy, and immunosuppression Evaluating thymic recovery in HIV-positive patients on highly active antiretroviral therapy Evaluating thymic output in patients with DiGeorge syndrome or other cellular immunodeficiencies Assessing the naive T-cell compartment in a variety of immunological contexts (autoimmunity, cancer, immunodeficiency, and transplantation) Identification of thymic remnants postthymectomy for malignant thymoma or as an indicator of relapse of disease (malignant thymoma) or other contexts of thymectomy

**Interpretation:** The absence or reduction of CD31+CD4 recent thymic emigrants (RTEs) generally correlates with loss or reduced thymic output and changes in the naive CD4 T-cell compartment, especially in infancy and prepubertal children. The CD4RTE result has to be interpreted more cautiously in adults due to age-related decline in thymic function and correlated with total CD4 T cell count and other relevant immunological data. CD4 RTEs measured along with TREC (TREC / T-Cell Receptor Excision Circles (TREC) Analysis, Blood) provides a comprehensive assessment of thymopoiesis, but should not be used in adults over the sixth decade of life as clinically meaningful information on thymic function is limited in the older population due to a physiological decline in thymic activity. To evaluate immune reconstitution or recovery of thymopoiesis post-T-cell depletion due to posthematopoietic cell transplant, immunotherapy, or other clinical conditions, it is helpful to systematically (serially) measure CD4RTE, and TREC copies in the appropriate age groups.

**Reference Values:**
**CD4 ABSOLUTE**
- **Males**
  - 1 month-17 years: 153-1,745 cells/mcL
  - 18-70 years: 290-1,175 cells/mcL
- Reference values have not been established for patients that are <30 days of age.
- Reference values have not been established for patients that are >70 years of age.
- **Females**
  - 1 month-17 years: 582-1,630 cells/mcL
  - 18-70 years: 457-1,766 cells/mcL
- Reference values have not been established for patients that are <30 days of age.
- Reference values have not been established for patients that are >70 years of age.

**CD4 RTE %**
- **Males**
  - 1 month-17 years: 19.4-60.9%
  - 18-25 years: 6.4-51.0%
  - 26-55 years: 6.4-41.7%
  - > or =56 years: 6.4-27.7%
- Reference values have not been established for patients that are <30 days of age.
- Reference values have not been established for patients that are >70 years of age.
- **Females**
  - 1 month-17 years: 25.8-68.0%
  - 18-25 years: 6.4-51.0%
  - 26-55 years: 6.4-41.7%
  - > or =56 years: 6.4-27.7%
- Reference values have not been established for patients that are <30 days of age.
Reference values have not been established for patients that are >70 years of age.

**CD4 RTE ABSOLUTE**

**Males**
- 1 month-17 years: 50.0-926.0 cells/μL
- 18-70 years: 42.0-399.0 cells/μL

Reference values have not been established for patients that are <30 days of age.

Reference values have not been established for patients that are >70 years of age.

**Females**
- 1 month-17 years: 170.0-1,007.0 cells/μL
- 18-70 years: 42.0-832.0 cells/μL

Reference values have not been established for patients that are <30 days of age.

Reference values have not been established for patients that are >70 years of age.

**Clinical References:**

**GLICP**

**89369**

**CD8 T-Cell Immune Competence Panel, Global**

**Clinical Information:**
CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is one of the early cytokines produced by CD8 T cells; it is released within a few hours of activation. The cytotoxic function is mediated by the contents of the cytolytic granules. Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate. CD8 T-cell activation occurs either through the T-cell receptor-peptide-Major-Histo Compatibility Complex or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of over-immunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid-organ transplant recipients, to prevent graft-versus-host disease in allogeneic hematopoietic stem cell transplant patients and to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of over-immunosuppression is a clinical challenge. Therapeutic drug monitoring is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. But, the levels of drugs measured in blood do not directly correlate with the administered dose due to individual pharmacokinetic differences. Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient's level of functional immune competence. This assay provides a means to evaluate over-immunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is
increased to halt or prevent graft rejection, to provide information on a balance between over-immunosuppression with subsequent infectious comorbidities and under-immunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8.30 a.m. and noon with no change between noon and afternoon. Natural killer-cell counts, on the other hand, are constant throughout the day. (4) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. (5-7) In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells. (5) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening (8) and during summer compared to winter. (9) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Determining over immunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

Interpretation: Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to over immunosuppression. IFN-gamma and CD107a and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

Reference Values:
The appropriate age-related reference values will be provided on the report.


GLIC

89317

CD8 T-Cell Immune Competence, Global, Blood

Clinical Information: CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is 1 of the early cytokines produced by CD8 T cells; it is released within a few hours of activation. (1) The cytotoxic function is mediated by the contents of the cytolytic granules. (1) Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate. (2) CD8 T-cell activation occurs either through the T-cell receptor (TCR)-peptide-major histocompatibility complex (MHC) or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of over-immunosuppression by therapeutic agents) results in reduced production of
IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and Thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid organ transplant recipients, to prevent graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplant patients and to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of over-immunosuppression is a clinical challenge. Therapeutic drug monitoring (TDM) is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. But, the levels of drugs measured in blood do not directly correlate with the administered dose due to individual pharmacokinetic differences.(3) Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient's level of functional immune competence. This assay provides a means to evaluate over-immunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is increased to halt or prevent graft rejection, to provide information on a balance between over-immunosuppression with subsequent infectious comorbidities and under-immunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. Natural Killer (NK) cell counts, on the other hand, are constant throughout the day.(4) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(5,6,7) In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells.(5) It is generally accepted that lower CD4 T cell counts are seen in the morning compared to the evening(8) and during summer compared to winter.(9) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Determining over immunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to overimmunosuppression. IFN-gamma and CD107a and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

**Reference Values:**

- Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%
- CD107a/b expression (as % CD8 T cells): 8.5-49.1%

Reference values have not been established for patients who are <19 years of age.

**Clinical References:**


CDH1Z

CDH1 Gene, Full Gene Analysis

Clinical Information: Hereditary diffuse gastric cancer (HDGC) is a rare autosomal dominant hereditary cancer syndrome associated with germline mutations in the CDH1 gene that encodes the protein E-cadherin. HDGC is predominantly characterized by increased susceptibility to diffuse gastric cancer and lobular breast cancer. HDGC is highly penetrant since the risk for developing gastric cancer is 80% by age 80. Women also have an approximately 40% to 60% risk of breast cancer by age 80. Colorectal cancer has been reported in individuals with germline CDH1 mutations however the specific lifetime risk for colorectal cancer is unknown. The International Gastric Cancer Linkage Consortium proposes clinical criteria for the selection of individuals who are at increased risk of having a germline CDH1 mutation as follows: 1) two or more cases of diffuse gastric cancer (histopathological confirmation in at least 1 case) in first- or second-degree relatives in which at least 1 individual is diagnosed prior to age 50; 2) three or more documented cases of diffuse gastric cancer in first- or second-degree relatives regardless of age of onset; 3) individuals diagnosed with diffuse gastric cancer before the age of 40 regardless of family history; 4) personal or family history of diffuse gastric cancer and lobular breast cancer in first and second relatives with at least 1 diagnosis occurring before age 50.

Useful For: Confirmation of suspected clinical diagnosis of hereditary diffuse gastric cancer Identification of familial CDH1 mutation to allow for predictive testing in family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


CDKZ

CDKN1C Gene, Full Gene Analysis

Clinical Information: Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Current data suggest that the etiology of BWS is due to dysregulation of imprinted genes in the 11p15 region of chromosome 11. Imprinting describes a difference in gene expression based on parent of origin. The majority of autosomal genes exhibit biallelic (maternal and paternal) expression, whereas imprinted genes normally express only 1 gene copy (either from the maternal or paternal allele). Imprinted genes are usually regulated by methylation, which prevents the gene from being expressed. Loss of expression or biallelic expression of an imprinted gene can lead to disease because of dosage imbalance. Some of the imprinted genes located in the region of 11p15 include H19 (maternally expressed), LIT1 (official symbol...
KCNQ1OT1 (paternally expressed), IGF2 (paternally expressed), and CDKN1C (aliases p57 and KIP2; maternally expressed). Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is due to inherited point mutations in CDKN1C in approximately 40% of cases. The etiology of sporadic cases includes:

- Hypomethylation of LIT1: approximately 50% to 60%
- Paternal uniparental disomy of chromosome 11: approximately 10% to 20%
- Hypermethylation of H19: approximately 2% to 7%
- Unknown: approximately 10% to 20%
- Point mutation in CDKN1C: approximately 5% to 10%
- Cytogenetic abnormality: approximately 1% to 2%
- Differentially methylated region 1 (DMR1) or DMR2 microdeletion: rare

The CDKN1C gene encodes a cyclin-dependent kinase inhibitor that acts as a negative regulator of cell proliferation and fetal growth. CDKN1C also functions as a tumor suppressor gene. Normally, CDKN1C is imprinted on the paternal allele and expressed only on the maternal allele. Absence of CDKN1C expression resulting from mutations of the maternally-inherited allele is postulated to contribute to the clinical phenotype of BWS. The appropriate first-tier test in the evaluation of a possible diagnosis of BWS is BWRS / Beckwith-Wiedemann Syndrome (BWS)/Russell-Silver Syndrome (RSS) Molecular Analysis. CDKZ / CDKN1C Gene, Full Gene Analysis should be ordered when results of BWS Methylation Analysis are negative and there is still a strong clinical suspicion of BWS. Mutations in the CDKN1C gene have also been linked to IMAGe syndrome (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita and genital anomalies). The CDKN1C mutations associated with IMAGe syndrome tend to be missense mutations occurring in the PCNA-binding domain of the gene.

**Useful For:** Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome
Confirming a clinical diagnosis of intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita and genital anomalies (IMAGe) syndrome

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CEBPA Mutations, Gene Sequencing**

**Clinical Information:** Acute myeloid leukemia (AML) with mutated CCAAT/enhancer-binding protein alpha gene (CEBPA) is a diagnostic category in the current WHO classification of hematopoietic neoplasms. In addition, CEBPA mutation on both alleles (so-called double mutation status) is considered a good prognostic feature in adults with newly diagnosed AML who have a normal karyotype or do not contain an alternate diagnostic genetic abnormality. Thus, evaluation for CEBPA mutations is necessary for accurate diagnosis in the current classification system and contributes prognostic information for a large group of AML patients.

**Useful For:** Initial evaluation of acute myeloid leukemia, both for assigning an appropriate diagnostic subclassification and as an aid for determining prognosis.
**Interpretation:** The results will be given as positive or negative for CEBPA mutation and, if positive, the mutation will be described and single or double mutation status will be indicated.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

**Cedar Red (Juniperus virginiana) IgE**

**Interpretation:** Class IgE (kU/L) Comment
- 0 <0.10 Negative
- 0.10-0.34 Equivocal/Borderline
- 0.35-0.69 Low
- 0.70-3.49 Moderate
- 3.50-17.49 High
- 17.50-49.99 Very High
- >49.99 Very Very High

**Reference Values:**
<0.35 kU/L

**Cedar, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
- 0 Negative
- 1 0.35-0.69 Equivocal
- 2 0.70-3.49 Positive
- 3 3.50-17.4 Positive

FCELG 57638

Celery IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

CELY 82766

Celery, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>
### Celiac Associated HLA-DQ Alpha 1 and DQ Beta 1 DNA Typing, Blood

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy) is mediated by T lymphocytes in patients with genetic susceptibility. This genetic association is with certain HLA genes in the class II region (DQ alpha 1, DQ beta 1). For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ typing and serology -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Assessing risk of celiac disease

**Interpretation:** Most (90%-95%) patients with celiac disease have 1 or 2 copies of HLA-DQ2 haplotype (see below), while the remainder have HLA-DQ8 haplotype. Rare exceptions to these associations have been occasionally seen. In 1 study of celiac disease, only 0.7% of patients with celiac disease lacked the HLA alleles mentioned above. Results are reported as permissive, nonpermissive, or equivocal gene pairs. It is important to realize that these genes are also present in about 20% of people without celiac disease. Therefore, the mere presence of these genes does not prove the presence of celiac disease or that genetic susceptibility to celiac disease is present. The HLA-DQ molecule is composed of two chains: DQ alpha (encoded by HLA-DQA1 gene) and DQ beta (encoded by HLA-DQB1 gene). HLA-DQ typing can be performed by serological or molecular methods. Currently most laboratories perform typing by molecular methods. HLA-DQ2 and DQ8 as typed by serology are usually based on the molecular typing of the DQB1 chain only. The current molecular method allows typing for both the DQB1 and DQA1 chains and this has shown that there are different haplotypes of HLA-DQ2 and DQ8. Typing of these haplotypes is important in celiac disease as they carry different risk association. There are 2 common haplotypes of DQ2: 1. DQA1*05:01 with DQB1*02:01 also called DQ2.5 in celiac literature 2. DQA1*02:01 with DQB1*02:02 also called DQ2.2 in celiac literature A single haplotype (heterozygote) of DQ2.5 is permissive for presence of celiac genes. However, only a double haplotype (homozygous) of DQ2.2 is permissive for presence of celiac genes. There are few reports where a single haplotype of DQ2.2 is considered to be an equivocal risk. In some cases the DQ2.2 haplotype maybe present with a DQ7.5 haplotype (DQA1*05:05 with DQB1*03:01). In this case a DQ2.5 molecule can be formed by the combination of DQB1*02:02 from 1 chromosome and DQA1*05:05 from the other chromosome. These cases fall in the same category as the DQ2.5 heterozygote. There are 3 common haplotypes of DQ8: 1. DQA1*03:01 with DQB1*03:02 2. DQA1*03:02 with DQB1*03:02 3. DQA1*03:03 with DQB1*03:02 Any single haplotype (heterozygote) of DQ8 is permissive for celiac. Therefore, the gene pairs permissive for celiac are: 1. Heterozygote (single copy) -DQA1*05:XX with DQB1*02:01 -DQA1*05:XX with DQB1*02:02 -DQA1*03:XX with DQB1*03:02 2. Homozygous (2 copies) -DQA1*02:01 with DQB1*02:02 Gene pairs equivocal for celiac are 1. Heterozygote (single copy) -DQA1*02:01 with DQB1*02:02 2. Rare alleleâ€™s types of DQ2 and DQ8 other than those listed above All other gene pair combinations are considered non-permissive for celiac.
Reference Values:
An interpretive report will be provided.


Celiac Disease Comprehensive Cascade

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy.(1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation.(2) Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type 1 diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers compared to approximately 40% of the general population.(3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy.(1-3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Comprehensive Cascade testing algorithm in Special Instructions). An individual suspected of having celiac disease may be HLA typed to determine if the individual has the susceptibility alleles DQ2 and/or DQ8.(4) In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient.(2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet.(1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves (see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions). This is typically accompanied by an improvement in clinical symptoms. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. - CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ typing and serology - CDSP / Celiac Disease Serology Cascade: complete serology testing excluding HLA DQ - CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet. To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease). It should be noted that HLA typing is not required to establish a diagnosis of celiac disease. Consider ordering CDSP / Celiac Disease Serology Cascade if HLA typing is not desired or has been previously performed.

Interpretation: Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range.
range. For these individuals both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; IgA-tTG, IgG-tTG, IgA-deamidated gliadin, and IgG-deamidated gliadin antibody assays are performed in this cascade. For individuals who have selective IgA deficiency with undetectable levels of IgA, only IgG-tTG and IgG-deamidated gliadin antibody assays are performed. HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA DQ2 allele; most of the remaining patients with celiac disease have the HLA DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. Individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, should be referred for small intestinal biopsy. HLA typing may be especially helpful for those patients who have begun to follow a gluten-free diet prior to a confirmed diagnosis of celiac disease.(4) Tissue Transglutaminase (tTG) Antibody, IgA/IgG: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for IgA-tTG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. For individuals with selective IgA deficiency, testing for IgG-tTG antibodies of the IgG isotype is performed. In these individuals, a positive IgG-tTG antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-tTG antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Antibody, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these individuals, a positive IgA-deamidated gliadin antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-deamidated gliadin antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial (EMA) Antibody, IgA: Positivity for EMA antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

**Reference Values:**

**IMMUNOGLOBULIN A (IgA)**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-&lt;5 months</td>
<td>7-37 mg/dL</td>
</tr>
<tr>
<td>5-&lt;9 months</td>
<td>16-50 mg/dL</td>
</tr>
<tr>
<td>9-&lt;15 months</td>
<td>27-66 mg/dL</td>
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<tr>
<td>15-&lt;24 months</td>
<td>36-79 mg/dL</td>
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<td>2-&lt;4 years</td>
<td>27-246 mg/dL</td>
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<tr>
<td>4-&lt;7 years</td>
<td>29-256 mg/dL</td>
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<tr>
<td>7-&lt;10 years</td>
<td>34-274 mg/dL</td>
</tr>
<tr>
<td>10-&lt;13 years</td>
<td>42-295 mg/dL</td>
</tr>
<tr>
<td>13-&lt;16 years</td>
<td>52-319 mg/dL</td>
</tr>
<tr>
<td>16-&lt;18 years</td>
<td>60-337 mg/dL</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>61-356 mg/dL</td>
</tr>
</tbody>
</table>

**HLA-DQ TYPING**

Presence of DQ2 or DQ8 alleles associated with celiac disease

**Interpretation:** HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA-DQ2 allele; most of the remaining patients with celiac disease have the HLA-DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. For these individuals, no further serologic testing is required. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. For individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, small intestinal biopsy is recommended.

Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable, but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease. Tissue Transglutaminase (tTG) Antibody, IgA/IgG: Individuals positive for tTG antibodies of the IgA and/or IgG isotype may have celiac disease and small intestinal biopsy is recommended. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Antibody, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA and/or IgG isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

**Clinical References:**
utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ typing and serology -CDSP / Celiac Disease Serology Cascade: complete serology testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for DQ2 and/or DQ8)

**Interpretation:** Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; IgA-tTG, IgG-tTG, IgA-deamidated gliadin, and IgG-deamidated gliadin antibody assays are performed in this cascade. For individuals who have selective IgA deficiency or undetectable levels of IgA, only IgG-tTG and IgG-deamidated gliadin antibody assays are performed. Tissue Transglutaminase (tTG) Ab, IgA/IgG: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG isotype is performed. In these individuals, a positive IgG-tTG antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-tTG antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Ab, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease; small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these individuals, a positive IgG-deamidated gliadin antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-deamidated gliadin antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial (EMA) Ab, IgA: Positivity for EMA antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease as antibody levels decrease over time in patients who have been following a gluten-free diet.

**Reference Values:**

| Immunoglobulin A |  
|------------------|---------------------------------------------------|
| 0-<5 months:     | 7-37 mg/dL                                         |
| 5-<9 months:     | 16-50 mg/dL                                        |
| 9-<15 months:    | 27-66 mg/dL                                        |
| 15-<24 months:   | 36-79 mg/dL                                        |
| 2-<4 years:      | 27-246 mg/dL                                       |
| 4-<7 years:      | 29-256 mg/dL                                       |
| 7-<10 years:     | 34-274 mg/dL                                       |
| 10-<13 years:    | 42-295 mg/dL                                       |
| 13-<16 years:    | 52-319 mg/dL                                       |
| 16-<18 years:    | 60-337 mg/dL                                       |
| > or =18 years:  | 61-356 mg/dL                                       |

Cell Count and Differential, Body Fluid

**Clinical Information:** Body fluids, other than the commonly analyzed urine and blood, include synovial, pleural, peritoneal, and pericardial fluids. These fluids may be present in increased volumes and/or may contain increased numbers of normal and/or abnormal cells in a variety of disease states.

**Useful For:** An aid in the diagnosis of joint disease, systemic disease, inflammation, malignancy, infection, and trauma

**Interpretation:** Trauma and hemorrhage may result in increased red and white cells; red cells predominate. White blood cells are increased in inflammatory and infectious processes: -Neutrophils predominate in bacterial infections -Lymphocytes predominate in viral infections -Macrophages may be increased in inflammatory and infectious processes -Eosinophils may be increased in parasitic or fungal infections

**Reference Values:**

**TOTAL NUCLEATED CELLS:**
- Synovial fluid: <150/mcL
- Peritoneal/pleural/pericardial fluid: <500/mcL

**NEUTROPHILS:**
- Synovial Fluid: <25%
- Peritoneal/pleural/pericardial fluid: <25%

**LYMPHOCYTES:**
- Synovial fluid: <75%

**MONOCYTES/MACROPHAGES:**
- Synovial fluid: 70%

**Clinical References:**

Cell-Bound Platelet Autoantibody, Solid Phase, Blood

**Clinical Information:** Platelet antibodies may be allo- or autoantibodies and may be directed to a wide range of antigenic "targets" on platelet cytoplasmic membranes. Alloantibodies are involved in clinical conditions such as platelet refractoriness, neonatal alloimmune thrombocytopenia, and posttransfusion purpura. In contrast, platelet autoantibodies are involved in idiopathic (autoimmune) thrombocytopenic purpura, the thrombocytopenia associated with systemic lupus erythematosus, and with the thrombocytopenia associated with sepsis (usually bacterial, occasionally fungal). Sometimes platelet autoantibodies can be detected in the patient's serum, but extensive data demonstrate that direct detection of immunologically bound immunoglobulin (usually IgG) is considerably more sensitive for autoantibody detection. The method consists of an elution step followed by solid-phase enzyme-linked immunosassay, which not only concentrates the cell-bound antibodies, but identifies the target glycoproteins against which they are directed. In most studies of autoimmune thrombocytopenia, the majority (approximately 80%) of detected autoantibodies were directed to the platelet glycoprotein IIb/IIIa and, more rarely, to other glycoproteins such as Ib/IX (approximately 11%) or Ia/IIa.

**Useful For:** Diagnosis of idiopathic (autoimmune) thrombocytopenic purpura Diagnosis of immune thrombocytopenia associated with systemic lupus erythematosus or other disorders associated with autoimmune phenomena

**Interpretation:** A positive test, particularly to GP IIB/IIIa or Ib/IX, in the presence of thrombocytopenia (not explained by other findings) is consistent with idiopathic (autoimmune) thrombocytopenic purpura. Similarly, a positive test in a thrombocytopenic patient with systemic lupus
erythematous is consistent with an autoimmune cause. Patients who are septic may also have a positive test with reactivity against most glycoproteins. Presence of reactivity to some glycoproteins has no clearly established clinical significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Cell-Free DNA Prenatal Screen**

**Clinical Information:** This test provides the ability to detect common chromosome abnormalities without the risk of pregnancy loss associated with invasive prenatal procedures. Chromosomal aneuploidy, that includes Down syndrome, trisomy 13, and trisomy 18, is the leading known genetic cause of miscarriage and congenital birth defects. Prenatal screening of fetal DNA is appropriate for pregnant patients with an increased risk for aneuploidy, including maternal age 35 or older at the time of delivery, abnormal fetal ultrasound findings indicating an increased risk for aneuploidy, a history of prior pregnancy with aneuploidy, positive maternal serum screening result, or a known parental balanced Robertsonian translocation. This fetal DNA screen is not a diagnostic test; therefore, abnormal results should be confirmed with invasive prenatal diagnostic testing (such as chorionic villi sampling or amniocentesis) and a genetic consultation is recommended. In addition, a negative result does not ensure an unaffected pregnancy. The false-negative rate for trisomy 21 is less than 1%, for trisomy 18 is 3.6%, and for trisomy 13 is 9.4%.(1) This screening test has not been sufficiently evaluated in pregnancies at low risk for aneuploidy or multiple gestation pregnancies and is not currently recommended for these populations.(1) The positive predictive value in low-risk pregnancies is lower than in pregnancies at high risk for aneuploidy.(2)

**Useful For:** Noninvasive screening for aneuploidies of chromosomes 13, 18, and 21 in high-risk pregnancies

**Interpretation:** Normal representation of material from chromosomes 13, 18, and 21 will be reported as normal, indicating a low risk for trisomy 13, trisomy 18, and trisomy 21 in the fetus. Fetal sex will be reported. If Y chromosome material is detected, this is suggestive of a male fetus. If Y chromosome material is not detected, this is suggestive of a female fetus. Increased amounts of chromosomal material will be reported as positive for having a trisomy of the identified chromosome. While most specimens undergoing this analysis can be readily characterized, on rare occasions equivocal or incidental results such as aneuploidy of chromosomes other than 13, 18, 21, as well as other genomic unbalanced rearrangements, may not allow for standard interpretation of this aneuploidy screen. In these situations, a new maternal blood specimen may be requested or a recommendation for other screening measures or diagnostic cytogenetic testing will be made.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
2. ACOG/SMFM Joint Committee Opinion: Noninvasive prenatal testing for fetal aneuploidy. No. 640, Dec 2015
5368

**Central Nervous System Consultation, Autopsy**

**Reference Values:**
This request will be processed as a consultation. Appropriate dissection will be performed and an interpretive report provided.

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CMA 9278

**Centromere Antibodies, IgG, Serum**

**Clinical Information:** Centromere antibodies occur primarily in patients with the calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) syndrome variant of systemic sclerosis (scleroderma). CREST syndrome is characterized by the following clinical features: calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia. (1)

Centromere antibodies were originally detected by their distinctive pattern of fine-speckled nuclear staining on cell substrates used in the fluorescent antinuclear antibody test. (2) In subsequent studies, centromere antibodies were found to react with several centromere proteins of 18 kDa, 80 kDa, and 140 kDa named as CENP-A, CENP-B, and CENP-C, respectively. (3) Several putative epitopes associated with these autoantigens have been described. The CENP-B antigen is believed to be the primary autoantigen and is recognized by all sera that contain centromere antibodies.

**Useful For:** Evaluating patients with clinical signs and symptoms compatible with systemic sclerosis including skin involvement, Raynaud phenomenon, and arthralgias As an aid in the diagnosis of calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) syndrome

**Interpretation:** In various reported clinical studies, centromere antibodies occur in 50% to 96% of patients with calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) syndrome. A positive test for centromere antibodies is strongly associated with CREST syndrome. The presence of detectable levels of centromere antibodies may antedate the appearance of diagnostic clinical features of CREST syndrome by several years.

**Reference Values:**
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

**Clinical References:**

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CENTA 110006

**Centromere Antibodies, Serum**

**Clinical Information:** Antinuclear antibodies are seen in a number of autoimmune disorders such as systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, Sjogren syndrome, and progressive systemic sclerosis. One autoantibody that produces a distinct staining pattern is the anticientromere antibody (ACA). ACA occurs in patients with the calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia (CREST) syndrome variant of progressive systemic sclerosis.

**Useful For:** Evaluation of patients with clinical signs and symptoms compatible with systemic sclerosis
**Interpretation:** A positive test for anticentromere antibody (ACA) is strongly associated with calcinosi, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia (CREST) syndrome. In various reported clinical studies, ACA occur in 50% to 96% of patients with CREST syndrome. The presence of detectable levels of ACA may antedate the appearance of diagnostic clinical features of CREST syndrome, in some cases by several years.

**Reference Values:**

<1:40 (Negative)


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**Cephalosporium acremonium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.

Ceramide Trihexosides and Sulfatides, Urine

Clinical Information: Urinary excretion of ceramide trihexosides and/or sulfatide can be suggestive of Fabry disease, metachromatic leukodystrophy, multiple sulfatase deficiency, mucolipidosis II (I-cell disease), or saposin B deficiency. Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. Individuals with Fabry disease, regardless of the severity of symptoms, may show an increased excretion of ceramide trihexoside in urine. Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the arylsulfatase A enzyme, which leads to the accumulation of various sulfatides in the brain, nervous system, and visceral organs, including the kidney and gallbladder. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Symptoms may include hypotonia, clumsiness, diminished reflexes, slurred speech, behavioral problems, and personality changes. Individuals with MLD typically show an increased excretion of sulfatides in urine. Low arylsulfatase A activity has been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatides is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with a fairly common polymorphism in the arylsulfatase A gene, which leads to low expression of the enzyme (5%-20% of normal). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD. Age of onset dictates the clinical subtypes of saposin B deficiency. Individuals with saposin B deficiency have normal arylsulfatase A activity. In urine, individuals with saposin B deficiency have an increased excretion of sulfatides and may also show increased excretion of ceramide trihexosides. Multiple sulfatase deficiency (MSD) is another rare autosomal recessive disorder that mimics the symptoms of MLD. In addition, individuals with MSD also may have clinical manifestations that resemble mucopolysaccharidoses. MSD results in deficiencies in all sulfatases including arylsulfatase A and B. Individuals with MSD have an increased excretion of sulfatides in their urine. Mucolipidosis II, also known as I-cell disease, is a rare autosomal recessive disorder with features of both mucopolysaccharidoses and sphingolipidoses. It is characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. This is a progressive disorder and death typically occurs in the first decade of life. Individuals with I-cell disease typically show an increased excretion of ceramide trihexosides and sulfatides in urine.

Useful For: Identifying patients with Fabry disease Identifying patients with metachromatic leukodystrophy Identifying patients with saposin B deficiency Identifying patients with multiple sulfatase deficiency Identifying patients with mucolipidosis II (I-cell disease)

Interpretation: No evidence of ceramide trihexosides or sulfatide accumulation suggests normal enzyme activities. Evidence of ceramide trihexoside accumulation suggests decreased or deficient alpha-galactosidase activity. Follow-up testing with the specific enzyme assay is recommended: -AGA / Alpha-Galactosidase, Leukocytes -AGABS / Alpha-Galactosidase, Blood Spot -AGAS / Alpha-Galactosidase, Serum Evidence of sulfatide accumulation suggests decreased or deficient arylsulfatase A activity. Follow-up with the specific enzyme assay is recommended: -ARSAW / Arylsulfatase A, Leukocytes -ARST / Arylsulfatase A, Fibroblasts -ARSU / Arylsulfatase A, 24 Hour, Urine To exclude multiple sulfatase deficiency (MSD), simultaneous determination of ARSB / Arylsulfatase B, Fibroblasts and I2SWS / Iduronate-2-sulfatase, Whole Blood (or I2SBS / Iduronate-2-sulfatase, Blood Spot) is recommended. Evidence of both ceramide trihexoside and sulfatide accumulation suggests diagnosis of mucolipidosis II (I-cell disease) or saposin B deficiency. Follow-up
testing to rule out I-cell disease may include: -NAGS / Hexosaminidase A and Total Hexosaminidase, Serum -AGAS / Alpha-Galactosidase, Serum, or ANAS / Alpha-N-Acetylglucosaminidase, Serum. Molecular genetic testing is required to confirm saposin B deficiency. See Fabry Disease Testing Algorithm in Special Instructions.

Reference Values:
An interpretive report will be provided.


SFIN 8009

Cerebrospinal Fluid (CSF) IgG Index

Clinical Information: Elevation of IgG levels in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (multiple sclerosis [MS], neurospherosis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to local central nervous system (CNS) synthesis of IgG. The 2 most commonly used diagnostic laboratory tests for MS are CSF index and oligoclonal banding. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases.

Useful For: As an aid in the diagnosis of multiple sclerosis

Interpretation: Cerebrospinal fluid (CSF) IgG index is positive (elevated) in approximately 80% of patients with multiple sclerosis (MS). Oligoclonal banding in CSF is also positive in approximately 80% of patients with MS. The use of CSF index plus oligoclonal banding has been reported to increase the sensitivity to over 90%. The index is independent of the activity of the demyelinating process.

Reference Values:
CSF index: 0.00-0.85
CSF IgG: 0.0-8.1 mg/dL
CSF albumin: 0.0-27.0 mg/dL
Serum IgG
0-4 months: 100-334 mg/dL
5-8 months: 164-588 mg/dL
9-14 months: 246-904 mg/dL
15-23 months: 313-1,170 mg/dL
2-3 years: 295-1,156 mg/dL
4-6 years: 386-1,470 mg/dL
7-9 years: 462-1,682 mg/dL
10-12 years: 503-1,719 mg/dL
13-15 years: 509-1,580 mg/dL
16-17 years: 487-1,327 mg/dL

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLabs.com
> or =18 years: 767-1,590 mg/dL
Serum albumin: 3,200-4,800 mg/dL
CSF IgG/albumin: 0.00-0.21
Serum IgG/albumin: 0.0-0.4
CSF IgG synthesis rate: 0-12 mg/24 hours


Ceruloplasmin, Serum

Clinical Information: Ceruloplasmin is a positive acute phase reactant and a copper-binding protein that accounts for >95% of serum copper in normal adults. Ceruloplasmin is measured primarily to assist with a diagnosis of Wilson disease. Other indications include Menkes disease, dietary copper insufficiency, and risk of cardiovascular disease. Wilson disease is a rare inherited disorder of copper transport that results in low serum copper and ceruloplasmin and accumulation of copper in various tissues. The pathological accumulation of copper in the liver, brain, cornea, and kidney cause cirrhosis, neuropsychiatric symptoms, Kayser-Fleischer rings, and hematuria/proteinuria, respectively. The Mayo Medical Laboratories Wilson disease testing algorithm (see Wilson Disease Testing Algorithm in Special Instructions) covers the appropriate use of clinical findings, serum biomarkers, genetic tests, and tissue biopsies when working up suspected cases. For additional background on Wilson disease testing see The Diagnosis of Wilson Disease in Publications. Menkes disease is an X-linked disorder in which dietary copper is absorbed from the gastrointestinal tract but cannot be transported, so copper is not available to the liver for incorporation into ceruloplasmin. Dietary ceruloplasmin deficiency may be due to inadequate dietary copper intake, long-term parenteral nutrition without copper supplementation, malabsorption, penicillamine therapy, or a combination of these.

Useful For: Investigation of patients with possible Wilson disease

Interpretation: Values <14 mg/dL are expected in Wilson disease. Values vary considerably from patient to patient and may be in the normal range in some patients with Wilson disease (indicating a different primary defect). Ceruloplasmin is a positive acute phase reactant. Increases in serum ceruloplasmin have been reported during pregnancy, in women taking oral contraceptives, in hepatitis, pneumonia, tuberculosis, rheumatoid arthritis, myocardial infarction, various forms of anemia and many obscure neurological disorders.

Reference Values:
Males
0-17 years: 14.0-41.0 mg/dL
> or =18 years: 15.0-30.0 mg/dL
Females
0-17 years: 14.0-41.0 mg/dL
> or =18 years: 16.0-45.0 mg/dL

80184  Cervical Papanicolaou Smear, Diagnostic without Physician Interpretation

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. The etiology of cervical carcinoma is unknown but the disease is believed to be related to sexual activity and possibly sexually transmitted viral infections such as human papillomavirus (HPV). Most cervical carcinomas and precancerous conditions occur in the transformation zone (squamo-columnar junction), therefore, this area needs to be sampled if optimum results are to be obtained.

Useful For: Screening for cervical carcinoma and a number of infections of the female genital tract including human papillomavirus, herpes, Candida, and Trichomonas

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

Note: Abnormal results will be reviewed by a physician at an additional charge.


8032  Cervical Papanicolaou Smear, Screening Without Physician Interpretation

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic, intraepithelial neoplastic, stages II in situ carcinoma, and eventually invasive carcinoma). This sequence is felt to develop over a matter of years in most patients. The etiology of cervical carcinoma is unknown but the disease is believed to be related to sexual activity and possibly sexually transmitted viral infections such as human papilloma virus. Most cervical carcinomas and precancerous conditions occur in the transformation zone (squamo-columnar junction), therefore, this area needs to be sampled if optimum results are to be obtained.

Useful For: Screening for cervical carcinoma and a number of infections of the female genital tract including human papillomavirus, herpes, Candida, and Trichomonas

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

Note: Abnormal results will be reviewed by a physician at an additional charge.


CFTRZ 35388  CFTR Gene, Full Gene Analysis

Clinical Information: Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. Clinical diagnosis is generally made based on these features, combined with a positive sweat chloride test or positive nasal potential difference. CF can also have an atypical presentation and
may manifest as congenital bilateral absence of the vas deferens (CBAVD), chronic idiopathic pancreatitis, bronchiectasis, or chronic rhinosinusitis. Several states have implemented newborn screening for CF, which identifies potentially affected individuals by measuring immunoreactive trypsinogen in a dried blood specimen collected on filter paper. If a clinical diagnosis of CF has been made, molecular testing for common CF mutations is available. To date, over 1,500 mutations have been described within the CF gene, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, deltaF508, accounts for approximately 67% of the mutations worldwide and approximately 70% to 75% in the North American Caucasian population. Most of the remaining mutations are rather rare, although some show a relatively higher prevalence in certain ethnic groups or in some atypical presentations of CF, such as isolated CBAVD. The recommended approach for confirming a CF diagnosis or detecting carrier status begins with molecular tests for the common CF mutations (eg, CFB / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel). This test, CFTR Gene, Full Gene Analysis may be ordered if 1 or both disease-causing mutations are not detected by the targeted mutation analysis (CFB / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel). Full gene analysis, sequencing and dosage analysis of the CFTR gene, is utilized to detect private mutations. Together, full gene analysis of the CFTR gene and deletion/duplication analysis identify over 98% of the sequence variants in the coding region and splice junctions. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least 1 copy of the G178R, G551S, G551D, S549N, S549R, G1244E, S1251N, S1255P, or G1349D mutation. See Cystic Fibrosis Molecular Diagnostic Testing Algorithm in Special Instructions for additional information.

**Useful For:** Follow-up testing to identify mutations in individuals with a clinical diagnosis of cystic fibrosis (CF) and a negative targeted mutation analysis for the common mutations Identification of mutations in individuals with atypical presentations of CF (eg, congenital bilateral absence of the vas deferens or pancreatitis) Identification of mutations in individuals where detection rates by targeted mutation analysis are low or unknown for their ethnic background Identification of patients who may respond to CFTR potentiator therapy This is not the preferred genetic test for carrier screening or initial diagnosis. For these situations, order CFB / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**Chaetomium globosum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
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Reference values apply to all ages.


Cheese American IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:

<0.35 kU/L

Cheese Cheddar IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Reference Values:

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Cheese Swiss IgE
**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**Cheese, Cheddar, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Cheese, Mold, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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patients (without a family history) and an odds ratio of 4.8 to 5.0 for individuals with a family history of breast cancer in a first- and second-degree relative. This suggests a moderate increase in breast cancer risk in women with a truncating CHEK2 mutation without a family history of breast cancer. These studies also suggest that truncating CHEK2 mutations are modifiers of breast cancer risk in the context of a positive family history of breast cancer. Some studies have also suggested an increased risk for colorectal cancer associated with germline CHEK2 mutations; however other studies have suggested that CHEK2 is not a major contributor to colorectal cancer risk.

**Useful For:** Evaluation for hereditary susceptibility to breast cancer or Li-Fraumeni-like syndrome

**Identification of a familial CHEK2 mutation to allow for predictive testing in family members**

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CHER 82798**

**Cherry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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CTRE
82607

Chestnut Tree, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Chestnut, Sweet, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**CHIC2 (4q12) Deletion (FIP1L1 and PDGFRA Fusion), FISH**

**Clinical Information:** Imatinib mesylate, a small molecule tyrosine kinase inhibitor from the 2-phenylaminopyrimidine class of compounds, has shown activity in the treatment of malignancies that are associated with the constitutive activation of a specific subgroup of tyrosine kinases. A novel tyrosine kinase, generated from fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRA gene, was identified in 9 of 16 patients (56%) with hypereosinophilic syndrome (HES). This fusion results from an approximate 800 kb interstitial chromosomal deletion that includes the cysteine-rich hydrophobic domain 2 (CHIC2) locus at 4q12. FIP1L1-PDGFRα is a constitutively activated tyrosine kinase that transforms hematopoietic cells, and is a therapeutic target for imatinib in a subset of HES patients. Mast cell disease (MCD) is a clinically heterogeneous disorder wherein accumulation of mast cells (MC) may be limited to the skin (cutaneous mastocytosis) or involve 1 or more extra-cutaneous organs (systemic MCD [SMCD]).
SMCD is often associated with eosinophilia (SMCD-eos). We recently tested the therapeutic activity of imatinib in 12 adults with SMCD-eos. In this study, we demonstrated that FIP1L1-PDGFRA is the therapeutic target of imatinib in the specific subset of patients with SMCD-eos. Furthermore, we provided evidence that the CHIC2 deletion is a surrogate marker for the FIP1L1-PDGFRA fusion.

**Useful For:** Providing genetic information for patients with hypereosinophilic syndrome (HES) and systemic mast cell disease (SMCD) involving CHIC2 deletion Identifying and tracking chromosome abnormalities and response to therapy

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range. Detection of an abnormal clone is usually associated with hypereosinophilic syndrome or systemic mastocytosis associated with eosinophilia. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Chick Pea, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Chicken Droppings, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Chicken Feathers, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Chicken IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Chicken Serum Proteins, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Chicken, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

**Useful For:** Aiding in the diagnosis of recent infection with Chikungunya virus in patients with recent travel to endemic areas and a compatible clinical syndrome

**Interpretation:**
- IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists.
- IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection. Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection.
- IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

**Reference Values:**
- IgM: Negative
- IgG: Negative
- Reference values apply to all ages.

**Clinical References:** Pan American Health Organization. Preparedness and Response for Chikungunya virus. Introduction into the Americas. Washington, DC, PAHO 2011

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**CHIKM 63867**

**Chikungunya IgM, Antibody, Serum**

**Reference Values:**
- Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

**CHIKI 37102**

**Chikungunya Interpretation**

**Reference Values:**
- Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

**FCVRQ 58028**

**Chikungunya Virus RNA, Qualitative Real-Time PCR**

**Reference Values:**
- Not Detected

**CHILI 82499**

**Chili Pepper, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Chimerism Transplant No Cell Sort

Clinical Information: Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

Useful For: Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

Interpretation: An interpretive report is provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

Reference Values: An interpretive report will be provided.

**CHIMS** 62984

**Chimerism Transplant Sorted Cells**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

**Interpretation:** An interpretive report is provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.


**CHIDB** 83182

**Chimerism-Donor**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success
**Interpretation:** An interpretive report is provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.


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**Chimerism-Recipient Germline (Pre)**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor’s and the recipient’s DNA prior to transplantation and then examining the recipient’s blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

**Interpretation:** An interpretive report is provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.


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**Chlamydia and Chlamydophila Antibody Panel 3 (IgG, IgA, IgM)**

**Reference Values:**
Reference Range:
- IgG <1:64
- IgA <1:16
- IgM <1:10

The immunofluorescent detection of specific antibodies to Chlamydia trachomatis, Chlamydophila pneumoniae, and C. psittaci may be complicated by crossreactive antibodies, non-specific antibody stimulation, or past exposure to more than one of these organisms. IgM titers of 1:10 or greater are
indicative of recent infection; however, IgM antibody is very crossreactive, often demonstrating titers to multiple organisms. Any IgG titer may indicate past exposure to that particular organism. Infection by a particular organism typically yields IgG titers that are higher than antibody titers to non-infecting organisms. IgA titers may help to identify the infecting organism when crossreactive IgG is present. IgA is typically present at low titers during primary infection, but may be elevated in recurrent exposures or in chronic infection.

**Chlamydia Pneumoniae PCR**

**Reference Values:**
- Not detected = Negative, no virus detected
- Detected = Positive, virus detected

This test employs PCR amplification and agarose gel electrophoresis detection of a Chlamydia pneumoniae-specific conserved genetic target. A positive result should be coupled with clinical indicators for diagnosis. A "Not detected" result for this assay does not exclude Chlamydia pneumoniae involvement in a disease process.

**Chlamydia Serology, Serum**

**Clinical Information:** Members of the family Chlamydiaceae are small, nonmotile, gram-negative, obligate intracellular organisms that grow in the cytoplasm of host cells. Two genera of clinical importance are Chlamydia, which includes Chlamydia trachomatis, and Chlamydia, which includes Chlamydomphila pneumoniae and Chlamydomphila psittaci. These organisms share many features of bacteria and are susceptible to antibiotic therapy. They are also similar to viruses, requiring living cells for multiplication. The chlamydial life cycle can be divided into 2 distinct phases: an extracellular, nonreplicating, infectious stage and an obligate intracellular, replicating, noninfectious stage. The infectious form, or elementary body (EB), attaches to the target cell membrane and enters the cell via a phagosome. After cell entry, the EB reorganizes into reticulate particles (forming inclusion bodies) and binary fission begins. After 18 to 24 hours, reticulate particles condense to form EBs. These new EBs are released, beginning another infection cycle. Chlamydomphila psittaci is the causative agent of psittacosis, a disease characterized by pneumonia, headache, altered mentation, and hepatosplenomegaly. Psittacosis is acquired by airborne transmission from infected birds. Chlamydomphila pneumoniae (formerly known as TWAR and, more recently, as Chlamydia pneumoniae) causes pneumonia in humans. It is unique because it is a primary pathogen of humans, is spread from human to human, and apparently has no animal or bird host. Chlamydomphila pneumoniae is responsible for approximately 10% of pneumonia cases. Chlamydia trachomatis has been implicated in a wide variety of infections in humans. It is a common cause of nongonococcal urethritis and cervicitis, and many systemic complications of chlamydial infections have been described. In females, this organism is a cause of pelvic inflammatory disease, salpingitis, and endometritis. In males, epididymitis and Reiter syndrome occur. Lymphogranuloma venereum is a sexually transmitted infection caused by Chlamydia trachomatis. It presents with a transient primary genital lesion followed by suppurative regional lymphadenopathy. Occasionally, severe proctitis or proctocolitis may develop. Chlamydia trachomatis also causes ophthalmologic infections, such as trachoma (rare in the United States), adult inclusion conjunctivitis and inclusion conjunctivitis in neonates. These disorders have traditionally been diagnosed by cytologic detection or culture. However, molecular detection methods (CTRNA / Chlamydia trachomatis by Nucleic Acid Amplification [GEN-PROBE]) may now represent a more sensitive diagnostic approach. Fitz-Hugh-Curtis syndrome (perihepatitis) has been associated with chlamydiae.

**Useful For:** Aids in the clinical diagnosis of chlamydial infections

**Interpretation:** IgG: Chlamydomphila pneumoniae > or =1:512 IgG endpoint titers of > or =1:512 are considered presumptive evidence of current infection. <1:512 and > or =1:64 A single specimen endpoint titer of > or =1:64 and <1:512 should be considered evidence of infection at an undetermined time. A second specimen drawn 10 to 21 days after the original draw should be tested in parallel with the first. If the second specimen exhibits a titer > or =1:512 or a 4-fold increase over that of the initial specimen,
current (acute) infection is indicated. Unchanging titers >1:64 and <1:512 suggest past infection. <1:64 IgG endpoint titers <1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. Chlamydia pneumoniae antibody is detectable in 25% to 45% of adults tested. Chlamydia psittaci and Chlamydia trachomatis > or =1:64 IgG endpoint titers of > or =1:64 are considered presumptive evidence of current infection. <1:64 IgG endpoint titers <1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. IgM Chlamydia pneumoniae, Chlamydia psittaci, and Chlamydia trachomatis > or =1:10 IgG endpoint titers of > or = 1:10 are considered presumptive evidence of infection. <1:10 IgG endpoint titers <1:10 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. IgM Chlamydia pneumoniae, Chlamydia psittaci, and Chlamydia trachomatis > or =1:10 IgM endpoint titers of > or = 1:10 are considered presumptive evidence of infection. <1:10 IgM endpoint titers <1:10 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels.

**Reference Values:**

- **Chlamydia pneumoniae**
  - IgG: <1:64
  - IgM: <1:10

- **Chlamydia psittaci**
  - IgG: <1:64
  - IgM: <1:10

- **Chlamydia trachomatis**
  - IgG: <1:64
  - IgM: <1:10

**Clinical References:**


**CGRNA 61553**

Chlamydia trachomatis and Neisseria gonorrhoeae by Nucleic Acid Amplification (GEN-PROBE)

**Clinical Information:** Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection (STI) in the United States. In 2010, 1.3 million documented cases were reported to the CDC. Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). Chlamydia trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, Chlamydia trachomatis may cause hepatitis and pharyngitis in adult. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual Chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI, with 301,174 cases of gonorrhea reported to CDC in
Like Chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence.). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae infection. However, these organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.

Immunoassays and nonamplification DNA tests are also available for Chlamydia trachomatis and Neisseria gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAATs. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis or Neisseria gonorrhoeae

**Interpretation:** A positive result indicates that rRNA of Chlamydia trachomatis and/or Neisseria gonorrhoeae is present in the specimen tested and strongly supports a diagnosis of chlamydial/gonorrheal infection. A negative result indicates that rRNA for Chlamydia trachomatis and/or Neisseria gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for Neisseria gonorrhoeae), if appropriate. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of indeterminate indicates that a new specimen should be collected. This test has not been shown to cross react with commensal (nonpathogenic) Neisseria species present in the oropharynx.

**Reference Values:**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia trachomatis</td>
<td>Negative</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Clinical References:**
Chlamydia trachomatis by Nucleic Acid Amplification (GEN-PROBE)

**Clinical Information:** Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection (STI) in the United States.(1,2) In 2010, 1.3 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). (2) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile.(2) Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). Chlamydia trachomatis can be transmitted from the mother during deliver and is associated with conjunctivitis and pneumonia. Finally, Chlamydia trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection.(2) Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure.(2) Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis infection.(2) However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(3-5) Immunoassays and nonamplification DNA tests are also available for Chlamydia trachomatis detection, but these methods are significantly less sensitive and less specific than NAATs.(2) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.(2) Improved detection rates result from both the increased performance of the assay. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis

**Interpretation:** A positive result indicates the presence of rRNA Chlamydia trachomatis. A negative result indicates that rRNA for Chlamydia trachomatis was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial or gonococcal urogenital infection, positive results should be carefully assessed and the patient retested by other methods, if appropriate.

**Reference Values:**
Negative

Chlamydia trachomatis Culture

Reference Values:
Not Isolated

Chlamydia trachomatis, Miscellaneous Sites, by Nucleic Acid Amplification (GEN-PROBE)

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection in the United States. In 2010, 1.3 million documented cases were reported to the CDC. Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). Chlamydia trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, Chlamydia trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual Chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis infection. However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for Chlamydia trachomatis detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detection of Chlamydia trachomatis

Interpretation: A positive result indicates the presence of rRNA Chlamydia trachomatis. This assay does detect plasmid-free variants of Chlamydia trachomatis. A negative result indicates that rRNA for Chlamydia trachomatis was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods, if appropriate.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention. 2014. Recommendations for the

**FCPC 90439**
Chlamyphila pneumoniae Culture
Reference Values:
Not Isolated

**FCPD 91750**
Chlamyphila pneumoniae DNA, Qualitative Real-Time PCR
Reference Values:
Reference Range: Not Detected

**FCHHY 57702**
Chloral Hydrate (Noctec)
Reference Values:
Trichloroethanol
Reference Range: 2 â€“ 12 ug/mL
Chloral Hydrate measured as trichloroethanol.
Chloral Hydrate is rapidly converted to trichloroethanol.

Test Performed by: Medtox Laboratories, Inc.
402 W. County Road D
St. Paul, MN 55112

**FCHLM 90343**
Chlordane and Metabolites, Serum/Plasma
Reference Values:
Reporting limit determined each analysis

Alpha-Chlordane
Synonym(s): Cis-Chlordane
Results reported in ppb

Gamma-Chlordane
Synonym(s): Trans-Chlordane
Results reported in ppb

Trans-Nonachlor
Synonym(s): Chlordane Component
Results reported in ppb

Heptachlorepoxide
Chlordiazepoxide and Metabolite, Serum

Clinical Information: Chlordiazepoxide (Librium) is a benzodiazepine widely used in the treatment of anxiety, alcohol withdrawal symptoms, and as a premedication for anesthesia. The mechanism of action of all benzodiazepines remains unclear. However, it is known that benzodiazepines facilitate gamma-aminobutyric acid (GABA)-mediated neurotransmission in the brain. Benzodiazepines most likely facilitate the inhibitory presynaptic or postsynaptic reactions of GABA. Chlordiazepoxide is metabolized to long-acting metabolites in the liver to the active metabolite nordiazepam (desmethyldiazepam) and the clearance of the drug is reduced considerably in the elderly and in patients with hepatic disease. Therapeutic assessment should include measurement of both the parent drug (chlordiazepoxide) and the active metabolite (nordiazepam).

Useful For: Monitoring chlordiazepoxide therapy Assessing toxicity Because chlordiazepoxide has a wide therapeutic index and dose-dependent toxicity, routine drug monitoring is not indicated in all patients

Interpretation: A therapeutic dose will yield a serum concentration of 1,000 to 3,000 ng/mL. Toxic concentration: >5,000 ng/mL

Reference Values:
Therapeutic concentration:
Chlordiazepoxide: 400-3,000 ng/mL
Nordiazepam: 100-500 ng/mL


Chloride, 24 Hour, Urine

Clinical Information: Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium (Na+). Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride (NaCl). However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

Useful For: As an indicator of fluid balance and acid-base homeostasis
**Interpretation:** Urine sodium and chloride excretion are similar and, under steady state conditions, both the urinary sodium and chloride excretion reflect the intake of NaCl. During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of NaHCO3) while urine chloride excretion remains appropriately low.

**Reference Values:**
40-224 mmol/24 hours


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**Chloride, Body Fluid**

**Reference Values:**
Not applicable

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, PA, 1994

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**Chloride, Random, Urine**

**Clinical Information:** Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium (Na⁺). Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride (NaCl). However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

**Useful For:** An indicator of fluid balance and acid-base homeostasis

**Interpretation:** Urine sodium and chloride excretion are similar and, under steady state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride (NaCl). During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of NaHCO3) while urine chloride excretion remains appropriately low.

**Reference Values:**
Interpret with other clinical data.

**Clinical Information:** Chloride (Cl) is the major anion in the extracellular water space; its physiological significance is in maintaining proper body water distribution, osmotic pressure, and normal anion-cation balance in the extracellular fluid compartment. Chloride is increased in dehydration, renal tubular acidosis (hyperchloremia metabolic acidosis), acute renal failure, metabolic acidosis associated with prolonged diarrhea and loss of sodium bicarbonate, diabetes insipidus, adrenocortical hyperfuction, salicylate intoxication and with excessive infusion of isotonic saline or extremely high dietary intake of salt. Hyperchloremia acidosis may be a sign of severe renal tubular pathology. Chloride is decreased in overhydration, chronic respiratory acidosis, salt-losing nephritis, metabolic alkalosis, congestive heart failure, Addisonian crisis, certain types of metabolic acidosis, persistent gastric secretion and prolonged vomiting, aldosteronism, bromide intoxication, syndrome of inappropriate antidiuretic hormone secretion, and conditions associated with expansion of extracellular fluid volume.

**Useful For:** Evaluation of water, electrolyte, and acid-base status

**Interpretation:** In normal individuals, serum chloride values vary little during the day, although there is a slight decrease after meals due to the diversion of chloride to the production of gastric juice.

**Reference Values:**
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L
Reference values have not been established for patients who are <12 months of age.

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, PA, 1994

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**Chloride, Spinal Fluid**

**Clinical Information:** Cerebrospinal fluid, which cushions the brain and spinal cord, is formed by both ultrafiltration and active secretion from plasma.

**Useful For:** This test is of limited clinical utility.

**Interpretation:** Cerebrospinal fluid chloride levels generally reflect systemic (blood) chloride levels.

**Reference Values:**
120-130 mmol/L

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**Chlorpromazine (Thorazine)**

**Reference Values:**
Reference Range: 30 – 300 ng/mL

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**Chocolate/Cacao IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of the quantitation for the assay. The clinical utility of food-specific IgG test has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Cholecystokinin (CCK)

Clinical Information: Cholecystokinin is a 33 amino acid peptide having a very similar structure to Gastrin. Cholecystokinin is present in several different sized forms including a 58 peptide Pro-CCK and 22, 12, and 8 peptide metabolites. The octapeptide retains full activity of the 33 peptide molecule. Cholecystokinin has an important physiological role in the regulation of pancreatic secretion, gallbladder contraction and intestinal motility. Cholecystokinin levels are elevated by dietary fat especially in diabetics. Elevated levels are seen in hepatic cirrhosis patients. Cholecystokinin is found in high levels in the gut, in the brain and throughout the central nervous system.

Reference Values:
Up to 80 pg/mL

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

Cholestanol

Reference Values:
0-8 weeks: 0.89 - 5.18 ug/mL (n=38)
>8 weeks: 0.86 - 3.71 ug/mL (n=68)


Cholesterol, BF

Clinical Information: Pleural Fluid: Quantitation of cholesterol in body fluids is clinically important and relevant in particular to the diagnosis of a cholesterol effusion. Cholesterol effusions (also known as pseudochylothorax or chyliform effusion) are important to differentiate from chylothorax, as their etiologies and therapeutic management strategies differ. Pseudochylylos or chyliform effusions accumulate gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema and by definition the effluent contains high concentrations of cholesterol. The fluid may have a milky or opalescent appearance and be similar to that of a chylous effusion, which contains high concentrations of triglycerides in the form of chylomicrons. An elevated cholesterol >250 mg/dL defines a cholesterol effusion in pleural fluid. Peritoneal Fluid: Ascites is the pathologic accumulation of excess fluid in the peritoneal cavity. Cholesterol analysis in peritoneal fluid may be a useful index to separate malignant ascites (>45-48 mg/dL) from cirrhotic ascites. Using a cutoff value of 48 mg/dL, the sensitivity, specificity, positive and negative predictive value, and overall diagnostic accuracy for differentiating malignant from nonmalignant ascites were reported as 96.5%, 96.6%, 93.3%, 98.3%, and 96.6%, respectively.(1) Synovial Fluid: Normal synovial fluid contains extremely low concentrations of lipids. Abnormalities in synovial fluid lipids may be attributed to cholesterol-rich pseudochylylos effusions which may be associated with chronic rheumatoid arthritis, lipid droplets due to traumatic injury and rarely due to severe chylous effusions associated with systemic lupus erythematosus, filariasis, pancreatitis, and trauma.(1) However, these diseases can usually be differentiated clinically and by gross and microscopic examination; quantification of lipids in synovial fluid only provides supporting information to the clinical picture.

Useful For: Distinguishing between chylous and nonchylous effusions Identifying iatrogenic effusions

Interpretation: Not applicable

Reference Values: Not applicable
Cholesterol, HDL, Serum

Clinical Information: High-density lipoprotein (HDL) is the smallest of the lipoprotein particles and comprises a complex family of lipoprotein particles that exist in a constant state of dynamic flux as the particles interact with other HDL particles and with low-density lipoprotein (LDL) particles and very-low-density lipoprotein (VLDL) particles. HDL has the largest proportion of protein relative to lipid compared to other lipoproteins (>50% protein). Total cholesterol levels have long been known to be related to coronary heart disease (CHD). HDL cholesterol is also an important tool used to assess an individual's risk of developing CHD since a strong negative relationship between HDL cholesterol concentration and the incidence of CHD has been reported. In some individuals, exercise increases the HDL cholesterol level; those with more physical activity have higher HDL cholesterol values.

Useful For: Cardiovascular risk assessment

Interpretation: Low high-density lipoprotein (HDL) cholesterol correlates with increased risk for coronary heart disease (CHD). Values > or =80 to 100 mg/dL may indicate metabolic response to certain medications such as hormone replacement therapy, chronic liver disease, or some form of chronic intoxication, such as with alcohol, heavy metals, or industrial chemicals including pesticides. HDL values < or =5 mg/dL occur in Tangier disease, in association with cholestatic liver disease, and in association with diminished hepatocyte function.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

HDL CHOLESTEROL
Males
> or =40 mg/dL
Females
> or =50 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17:

HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline low: 40-45 mg/dL
Acceptable: >45 mg/dL

**Cholesterol, Total, Serum**

**Clinical Information:** Cholesterol is a steroid with a secondary hydroxyl group in the C3 position. It is synthesized in many types of tissue, but particularly in the liver and intestinal wall. Approximately 75% of cholesterol is newly synthesized and 25% originates from dietary intake. Normally, the cholesterol in the plasma or serum is 60% to 80% esterified. Approximately 50% to 75% of the plasma cholesterol is transported by low-density lipoproteins (LDL) and 15% to 40% by high-density lipoproteins (HDL). Serum cholesterol is elevated in the hereditary hyperlipoproteinemias and in various other metabolic diseases. Moderate-to-markedly elevated values are also seen in cholestatic liver disease. Hypercholesterolemia reflects an increase of lipoproteins of 1 or more specific classes (eg, beta-LDL, alpha-1 HDL, alpha-2 HDL, or LP-X). Hypercholesterolemia is a risk factor for cardiovascular disease. Low levels of cholesterol can be seen in disorders that include hyperthyroidism, malabsorption, and deficiencies of apolipoproteins.

**Useful For:** Evaluation of cardiovascular risk

**Interpretation:** The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for total cholesterol: Desirable: <200 mg/dL Borderline high: 200 to 239 mg/dL High: > or =240 mg/dL Values above the normal range indicate a need for quantitative analysis of the lipoprotein profile. Values in hyperthyroidism usually are in the lower normal range; malabsorption values may be <100 mg/dL, while beta-lipoprotein or apolipoprotein B deficiency values usually are <80 mg/dL. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

**TOTAL CHOLESTEROL**
- Desirable: <200 mg/dL
- Borderline high: 200-239 mg/dL
- High: > or =240 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children 2 to 17 years of age:

**TOTAL CHOLESTEROL**
- Acceptable: <170 mg/dL
- Borderline high: 170-199 mg/dL
- High: > or =200 mg/dL

**Clinical References:**

**Cholesteryl Esters, Serum**

**Clinical Information:** Cholesterol in the blood serum normally is 60% to 80% esterified with fatty acids, largely as a result of the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which circulates in the blood in association with the high-density lipoproteins. LCAT transfers an acyl group for lecithin to cholesterol. Familial deficiency of LCAT is uncommon, usually occurring individuals of northern Europe descent, and is associated with erythrocyte abnormalities (target cells) and decreased (20% or less) esterification of plasma cholesterol. This is associated with early atherosclerosis, corneal opacification, hyperlipidemia, and mild hemolytic anemia. Persons with liver disease may have impaired
formation of LCAT and, therefore, a secondary deficiency of this enzyme and of esterified plasma cholesterol.

**Useful For:** Establishing a diagnosis of lecithin-cholesterol acyltransferase deficiency Evaluating the extent of metabolic disturbance by bile stasis or liver disease

**Interpretation:** In patients with lecithin-cholesterol acyltransferase deficiency, the concentration of unesterified cholesterol in serum may increase 2 to 5 times the normal value, resulting in a decrease in esterified serum cholesterol to 20% or less of the total serum cholesterol.

**Reference Values:**
60-80% of total cholesterol

Reference values have not been established for patients that are <16 years of age.


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**Chromatin (Nucleosomal) Antibody**

**Reference Values:**
Reference Range: <1.0 Negative AI

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**Chromium for Occupational Monitoring, Urine**

**Clinical Information:** Chromium (Cr) has an atomic mass of 51.996, atomic number 24, and valences ranging from 2(-) to 6(+). Hexavalent chromium, Cr(6+), and trivalent chromium, Cr(3+), are the 2 most prevalent forms. Cr(3+) is the only oxidation state present under normal physiologic conditions. Cr(6+) is widely used in industry to make chromium alloys including stainless steel pigments and electroplated coatings. Cr(6+), a known carcinogen, is rapidly metabolized to Cr(3+). Cr(3+) is the only form present in human urine.

**Useful For:** Screening for occupational exposure

**Interpretation:** The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively (Section 3.3.1).

**Reference Values:**
Chromium/creatinine ratio: <10.0 mcg/g creatinine


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**Chromium, 24 Hour, Urine**

**Clinical Information:** Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[6+]) and trivalent chromium (Cr[3+]) are the 2 most prevalent forms. Cr[6+] is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr[6+], a known carcinogen, is immediately converted to Cr[3+] upon exposure to biological tissues. Cr[3+] is the only chromium species found in biological specimens. Urine chromium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced...
by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Screening for occupational exposure to chromium Monitoring metallic prosthetic implant wear

**Interpretation:** Chromium is principally excreted in the urine. Urine levels correlate with exposure. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (8-16 mcg/24 hour) in urine chromium concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations >20 mcg/24 hour in a patient with chromium-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. A test for this specific purpose (CHROMU / Chromium for Occupational Monitoring, Urine) is available.

**Reference Values:**

- 0-15 years: not established
- > or =16 years: 0.0-7.9 mcg/specimen

**Clinical References:**


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**Chromium, Random, Urine**

**Clinical Information:** Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[+6]) and trivalent chromium (Cr[+3]) are the 2 most prevalent forms. Cr[+6] is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr[+6], a known carcinogen, is immediately converted to Cr[+3] upon exposure to biological tissues. Cr[+3] is the only chromium species found in biological specimens. Urine chromium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Screening for occupational exposure to chromium Monitoring metallic prosthetic implant wear

**Interpretation:** Chromium is principally excreted in the urine. Urine levels correlate with exposure. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (8-16 mcg/L) in urine chromium concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations >20 mcg/L in a patient with chromium-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase...
in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. A test for this specific purpose (CHROMU / Chromium for Occupational Monitoring, Urine) is available.

**Reference Values:**
No established reference values


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**Chromium, Serum**

**Clinical Information:** Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[+6]) and trivalent chromium (Cr[+3]) are the 2 most prevalent forms. Cr(+6) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(+6), a known carcinogen, is immediately converted to Cr(+3) upon exposure to biological tissues. Cr(+3) is the only chromium species found in biological specimens. Serum Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Screening for occupational exposure Monitoring metallic prosthetic implant wear

**Interpretation:** Results greater than the flagged value indicate clinically significant exposure to chromium (Cr) (see Cautions about specimen collection). Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (0.3-0.6 ng/mL) in serum Cr concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations >1 ng/mL in a patient with Cr-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
<0.3 ng/mL
When collected by a phlebotomist experienced in ultra-clean collection technique and handled according to the instructions in Trace Metals Analysis Specimen Collection and Transport in Special Instructions, we have observed the concentration of chromium in serum to be <0.3 ng/mL. However, the majority of specimens submitted for analysis from unexposed individuals contain 0.3-0.9 ng/mL of chromium. Commercial evacuated blood collection tubes not designed for trace-metal specimen collection yield serum containing 2.0-5.0 ng/mL chromium derived from the collection tube.


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**Chromogranin A, Serum**

**Clinical Information:** Chromogranin A (CGA) is a 439-amino acid protein with a molecular weight of 48 to 60 kDa, depending on glycosylation and phosphorylation status. It is a member of the granin family of proteins and polypeptides. Granins are widespread in endocrine, neuroendocrine, peripheral, and
Carcinoid Tumors: CGA is elevated in most patients (approximately 90%) with symptomatic or advanced carcinoids (carcinoid syndrome), usually to levels several times the upper limit of the reference interval. CGA is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. To achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serum CGA, serotonin in serum or blood, and 5-HIAA in urine should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can usually be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests such as pancreastatin, vasostatin, and catestatin, while others are less well characterized. Because of its ubiquitous distribution within neuroendocrine tissues, CGA can be a useful diagnostic marker for neuroendocrine neoplasms, including carcinoids, pheochromocytomas, medullary thyroid carcinomas (MTC), some pituitary tumors, functioning and nonfunctioning islet cell tumors and other amine precursor uptake and decarboxylation (APUD) tumors. It can also serve as a sensitive means for detecting residual or recurrent disease in treated patients. Carcinoid tumors in particular almost always secrete CGA along with a variety of specific modified amines, chiefly serotonin (5-hydroxytryptamine: 5-HT) and peptides. 

Useful For: Follow-up or surveillance of patients with known or treated carcinoid tumors. An adjunct in the diagnosis of carcinoid tumors. An adjunct in the diagnosis of other neuroendocrine tumors, including pheochromocytomas, medullary thyroid carcinomas, functioning and nonfunctioning islet cell and gastrointestinal amine precursor uptake and decarboxylation tumors, and pituitary adenomas. A possible adjunct in outcome prediction and follow-up in advanced prostate cancer.

Interpretation: Follow-up/Surveillance: Urine 5-hydroxyindolacetic acid (5-HIAA) and serum chromogranin A (CGA) increase in proportion to carcinoid tumor burden. Because of the linear relationship of CGA to tumor burden, its measurement also provides prognostic information. Most mid- and hindgut tumors secrete CGA even if they do not produce significant amounts of serotonin or serotonin metabolites (5-HIAA). Guidelines recommend 3 to 12 monthly measurements of CGA or 5-HIAA in follow-up of midgut carcinoids. Patients with foregut tumors can also be monitored with CGA or 5-HIAA measurements, if they were positive for these markers at initial diagnosis. Hindgut tumors usually do not secrete serotonin, and consequently only CGA monitoring is recommended. As is typical for tumor marker use in follow-up and surveillance, a 40% to 50% change in serum CGA concentrations should be considered potentially clinically significant in the absence of confounding factors (see Cautions). Much smaller changes in CGA concentrations might be considered significant if they occur over several serial measurements and are all in the same direction. Adjunct in Diagnosis of Carcinoid Tumors: CGA is elevated in most patients (approximately 90%) with symptomatic or advanced carcinoids (carcinoid syndrome), usually to levels several times the upper limit of the reference interval. Serum CGA measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. CGA is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. To achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serum CGA, serotonin in serum or blood, and 5-HIAA in urine should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can usually be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests such
as urine serotonin measurement will be required. An example would be a foregut tumor, which does not secrete CGA and only produces 5-hydroxytryptophan (5-HTP), rather than serotonin. In this case, circulating chromogranin, serotonin, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels. Adjunct in the Diagnosis of Other Neuroendocrine Tumors: In patients with suspected neuroendocrine tumors other than carcinoids, CGA is often elevated alongside any specific amine and peptide hormones or neurotransmitters that may be produced. The CGA elevations are less pronounced than in carcinoid tumors, and measurement of specific tumor secretion products is considered of greater utility. However, CGA measurements can occasionally aid in diagnosis of these tumors if specific hormone measurements are inconclusive. This is the case in particular with pheochromocytoma and neuroblastoma, where CGA levels may be substantially elevated and can, therefore, provide supplementary and confirmatory information to measurements of specific hormones. In particular, CGA measurements might provide useful diagnostic information in patients with mild elevations in catecholamines and metanephrines;(6) such mild elevations often represent false-positive test results. Possible Adjunct in Outcome Prediction and Follow-up of Prostate Cancer: Prostate cancers often contain cells with partial neuroendocrine differentiation. These cells secrete CGA. The amounts secreted are insufficient in most cases to make this a useful marker for prostate cancer diagnosis. However, if patients with advanced prostate cancer are found to have elevated CGA levels, this indicates the tumor contains a significant neuroendocrine cell subpopulation. Such tumors are often resistant to antiandrogen therapy and have a worse prognosis. These patients should be monitored particularly closely.(5)

Reference Values:
<93 ng/mL
Reference values apply to all ages.


Chromosomal Microarray (CMA) Familial Testing, FISH

Clinical Information: Chromosomal microarray (CMA) is a method for detecting copy number changes (gains or losses) across the entire genome. When copy number changes are identified in a patient, parental studies are sometimes necessary to assess their clinical significance. Changes that are inherited from clinically normal parents are less likely to be clinically significant in the patient and de novo changes are more likely to be pathogenic. To identify familial copy number changes in parents of previously tested patients, FISH testing is utilized. The parental results will provide the context for interpretation of the patient's CMA results.

Useful For: Determining the inheritance pattern of copy number changes previously identified by
chromosomal microarray analysis in a patient and aiding in the clinical interpretation of the pathogenicity of the copy number change.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Chromosomal Microarray, Autopsy, Products of Conception, or Stillbirth**

**Clinical Information:** Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of products of conception (POC), a stillborn infant, or neonate (autopsy) may provide useful information concerning the cause of fetal loss. In addition, CMA may provide information regarding the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages or when fetal malformations are evident. CMA is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excess homozygosity on a single chromosome could suggest uniparental disomy that may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excess homozygosity on multiple chromosomes may suggest consanguinity.

**Useful For:** Prenatal diagnosis of copy number changes (gains or losses) across the entire genome
Diagnosing chromosomal causes for fetal death
Determining recurrence risk of future pregnancy losses
Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies
Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray
Assessing regions of homozygosity related to uniparental disomy or identity by decent.

**Interpretation:** Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. The detection of excess homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders present in regions of homozygosity.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CMACB 35247**

**Chromosomal Microarray, Congenital, Blood**

**Clinical Information:** Aneuploidy or unbalanced chromosome rearrangements are often found in patients with intellectual disability, developmental delay, autism, dysmorphic features, or congenital anomalies. Some chromosomal abnormalities are large enough to be detected with conventional chromosome analysis. However, many pathogenic rearrangements are below the resolution limits of chromosome analysis (approximately 5 megabases). Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions of excessive homozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy (UPD), which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders associated with UPD. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity and, therefore, could be useful in determining candidate genes for further testing for autosomal recessive disorders. As a participant in the International Standard Cytogenomic Array Consortium (ISCA) (see Chromosomal Microarray Testing and the ISCA Consortium Database in Special Instructions), Mayo Clinic Cytogenetics Laboratory contributes submitted clinical information and test results for molecular cytogenetic tests to a HIPAA-compliant, deidentified public database hosted by the National Institute of Health. This is an international effort to improve diagnostic testing and our understanding of the relationships between genetic changes and clinical symptoms (for information about the database visit the consortium website at https://www.iscaconsortium.org). Confidentiality of each specimen is maintained. Patients may request to opt-out of this scientific effort by calling the laboratory at 800-533-1710, extension 8-2952, and asking to speak with a laboratory genetic counselor. Please call with any questions.

**Useful For:** First-tier, postnatal test for individuals with multiple anomalies that are not specific to well-delineated genetic syndromes, apparently nonsyndromic developmental delay or intellectual disability, or autism spectrum disorders as recommended by the American College of Medical Genetics (ACMG). An appropriate follow-up test for individuals with unexplained developmental delay or intellectual disability, autism spectrum disorders, or congenital anomalies with a previously normal conventional chromosome study Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray. Assessing regions of homozygosity related to uniparental disomy or identity by descent.

**Interpretation:** When interpreting results, the following factors need to be considered: Copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether
the change is a deletion or duplication, the inheritance pattern, and the clinical and/or developmental history of a transmitting parent. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Families benefit from hearing genetic information multiple times and in multiple ways. A referral to a clinical genetics professional is appropriate for individuals and families to discuss the results of chromosomal microarray testing.

Reference Values:
An interpretive report will be provided.


Chromosomal Microarray, Hematologic Disorders

Clinical Information: The importance of identifying chromosome abnormalities in hematologic disorders is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can do the following: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Detection and characterization of clonal copy number imbalance and loss of heterozygosity associated with hematologic neoplasms Assisting in the diagnosis and classification of certain hematologic neoplasms Evaluating the prognosis for patients with certain hematologic neoplasms

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen
collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling**

**Clinical Information:** Chromosomal abnormalities cause a wide range of disorders associated with birth defects and intellectual disability. Many of these disorders can be diagnosed prenatally by analysis of chorionic villi or amniocytes. The most common reasons for performing cytogenetic studies for prenatal diagnosis include advanced maternal age, abnormal prenatal screen, a previous child with a chromosome abnormality, abnormal fetal ultrasound, or a family history of a chromosome abnormality. Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the chromosomal microarray as a replacement for the fetal karyotype in patients with a pregnancy demonstrating 1 or more major structural abnormalities on ultrasound when undergoing invasive prenatal diagnosis.(1) This CMA test utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy, which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity.

**Useful For:**
- Prenatal diagnosis of copy number changes (gains or losses) across the entire genome
- Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies
- Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray
- Assessing regions of homozygosity related to uniparental disomy or identity by descent.

**Interpretation:** Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. When interpreting results it is important to realize that copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance
pattern, and the clinical and developmental history of a transmitting parent. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Copy number changes with unknown significance will be reported when at least 1 gene is involved in a deletion >1 megabases (Mb) or a duplication >2 Mb. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Regions with absence of heterozygosity (AOH) with unknown significance will be reported when >10 Mb. Whole genome AOH will be reported when >10% of the genome.

Reference Values:
An interpretive report will be provided.


Chromosomal Microarray, Tumor, FFPE

Clinical Information: The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes copy number probes and single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 50 to 100 kilobases. CMA can: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes -The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Genomic characterization of tumor for copy number imbalances and loss of heterozygosity Assisting in the diagnosis and classification of malignant neoplasms Evaluating the prognosis for patients with malignant tumors

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen...
collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties. See Cytogenetic Analysis of Glioma in Special Instructions for common questions and answers.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CMAT 35900**

**Chromosomal Microarray, Tumor, Fresh or Frozen using Affymetrix Cytoscan HD®**

**Clinical Information:** The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes. The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

**Useful For:** Genomic characterization of tumor for copy number imbalances and loss of heterozygosity, Assisting in the diagnosis and classification of malignant neoplasms, including hematolymphoid malignancies Evaluating the prognosis for patients with malignant tumors

**Interpretation:** The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasm, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

**Reference Values:**
An interpretive report will be provided.

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**CHRAF**  
**35243**  
**Chromosome Analysis, Amniotic Fluid**

**Clinical Information:** Chromosome analysis for prenatal diagnosis is appropriate in pregnancies with apparent birth defects, ultrasound markers, abnormal maternal screening, advanced maternal age, and features suggestive of or concerns for aneuploidy syndromes, including Down syndrome, Turner syndrome, Klinefelter syndrome, Trisomy 13 syndrome, and Trisomy 18 syndrome. Chromosomal abnormalities are the cause of a wide range of disorders associated with birth defects and congenital diseases. Many of these disorders can be diagnosed prenatally by analysis of amniocytes. This method permits diagnosis of chromosome abnormalities during the second trimester of pregnancy or later. The most common reasons for cytogenetic studies for prenatal diagnosis include advanced maternal age, abnormal maternal serum screen, a previous child with a chromosome abnormality, abnormal fetal ultrasound, or a family history of a chromosome abnormality.

**Useful For:** Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy), structural abnormalities and balanced rearrangements

**Interpretation:** Cytogenetic studies on amniotic fluid are considered nearly 100% accurate for the detection of large fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions usually can be detected only with the use of targeted FISH testing. Approximately 3% of amniotic fluid specimens analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and other environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis prior to performing the amniocentesis. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

**Reference Values:**  
An interpretative report will be provided.


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**CHRPC**  
**35315**  
**Chromosome Analysis, Autopsy, Products of Conception, or Stillbirth**

**Clinical Information:** Chromosome analysis of products of conception, spontaneous abortions, stillborn infants, or neonates is appropriate when previous losses have occurred and in pregnancies with apparent birth defects, ultrasound markers, abnormal maternal screening, advanced maternal age, and features suggestive of or concerns for aneuploidy syndromes, including Down syndrome, Turner syndrome, Klinefelter syndrome, trisomy 13 syndrome and trisomy 18 syndrome. Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneous abortuses range from 15% to 60%. Chromosome studies of products of conception (POC) may provide useful information concerning the cause of miscarriage and, thus, the recurrence risk for pregnancy loss and risk for having subsequent children with chromosome anomalies. Chromosome analysis of the stillborn infant or neonate (autopsy)
may be desirable, particularly if there is a family history of 2 or more miscarriages or when malformations are evident. For neonatal cases, peripheral blood is the preferred specimen for chromosome analysis (CHRCB / Chromosome Analysis, Congenital Disorders, Blood). The finding of a chromosome abnormality may explain the cause of a miscarriage or stillbirth, particularly when the chromosome results show aneuploidy or an unbalanced structural rearrangement. Some of the chromosome abnormalities that are detected in these specimens are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects, miscarriage, or stillbirth. For balanced chromosome rearrangements, it is sometimes difficult to determine whether the chromosome abnormality is the direct cause of a miscarriage or stillbirth. In these situations, chromosome studies of the parents’ peripheral blood may be useful to determine if an abnormality is familial or de novo. De novo, balanced rearrangements can cause miscarriages or stillbirth by producing submicroscopic deletions, duplications, or gene mutations at the site of chromosome breakage. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). Subtle structural chromosomal abnormalities can occasionally be missed.

Useful For: Diagnosis of congenital chromosome abnormalities in products of conception, including aneuploidy (ie, trisomy or monosomy) and structural abnormalities

Interpretation: A normal result is a karyotype of 46,XX or 46,XY. A chromosome abnormality known to be pathogenic will be reported as abnormal. Apparently balanced rearrangements will be reported. On rare occasions, structural changes with unknown clinical significance will be identified and reported. Due to bacterial contamination or nonviable cells, we are unable to establish a viable culture 20% of the time. In these cases, the specimen cannot be used for chromosome analysis, and the FISH aneuploidy test (POCR / Aneuploidy Detection, Products of Conception [POC], FISH) is automatically initiated. While the FISH test is not as comprehensive as a chromosome analysis, it can provide information with regard to the most common numeric abnormalities in spontaneous miscarriage and stillbirth. A FISH signal pattern with 2 signals for 13, 15, 16, 18, 21, 22 and either 2 signals for chromosome X or one signal for chromosome X and one signal for chromosome Y in each interphase will be reported as normal. A FISH signal pattern indicating an additional signal (3 signals) in each interphase will be reported as having a trisomy of the chromosome identified. A FISH signal pattern indicating loss of a signal (1 signal) will be reported as having a monosomy of the chromosome identified. A FISH signal pattern indicating an additional signal for every chromosome (3 signals for X and/or Y and 3 signals for chromosomes 13, 15, 16, 18, 21, 22) will be reported as having triploidy.

Reference Values: An interpretive report will be provided.


CHRBF 35314

Chromosome Analysis, Body Fluid

Clinical Information: Cytogenetic studies on body fluids (eg, pleural effusions, ascites, and pericardial, cerebrospinal, and synovial fluids) may be helpful to diagnose or to rule-out metastases or relapses in patients with lymphoma or other malignancies. Chromosome analysis serves as a useful adjunct to cytology. In pleural fluids, lymphomas are often more readily diagnosed by cytogenetic techniques than by standard cytologic examination.

Useful For: Assisting in the diagnosis of certain malignancies

Interpretation: The observation of a chromosomally abnormal clone is evidence of a clonal neoplastic process. A normal karyotype does not eliminate the possibility of a neoplastic process. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended.

Reference Values:
An interpretive report will be provided.


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**CHRCV 35251**

**Chromosome Analysis, Chorionic Villus Sampling**

**Clinical Information:** Although not used as widely as amniocentesis, the use of chorionic villus sampling (CVS) for chromosome analysis is an important procedure for the prenatal diagnosis of chromosome abnormalities. CVS can be collected by either transcervical or transabdominal techniques. The medical indications for performing chromosome studies on CVS are similar to amniocentesis, and may include advanced maternal age, abnormal first trimester screen, history of a previous child with congenital anomalies, abnormal fetal ultrasound, and family history of a chromosome abnormality.

**Useful For:** Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy), structural abnormalities, and balanced rearrangements

**Interpretation:** Cytogenetic studies on chorionic villus specimen (CVS) are considered more than 99% reliable for the detection of most fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions usually can be detected only with the use of targeted FISH testing. Approximately 3% of CSVs analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis before the procedure is performed, so that patients may make an informed decision about pursuing the procedure. Limitations: -False-chromosome mosaicism may occur due to artifact of culture -True mosaicism may be missed due to statistical sampling error -Presence of chromosome abnormalities in placental cells that do not occur in cells of the fetus (confined placental mosaicism) -Subtle structural chromosome abnormalities can occasionally be missed It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CHRCB 35248**

**Chromosome Analysis, Congenital Disorders, Blood**

**Clinical Information:** Chromosome analysis is appropriate for individuals with clinical features including infertility, multiple miscarriages, delayed puberty, ambiguous genitalia, amenorrhea, intellectual disability, mental retardation, developmental delay, autism, dysmorphic features, birth defects, behavior disorders, learning disability, cognitive impairment, or individuals with clinical features suggestive of an aneuploidy syndrome, including Down syndrome, Turner syndrome, Klinefelter syndrome, Trisomy 13 syndrome, and Trisomy 18 syndrome. Chromosome abnormalities cause a wide range of disorders associated with birth defects and congenital diseases. Congenital chromosome studies are done on blood for a wide variety of indications including mental retardation, failure to thrive, possible Down syndrome, delayed puberty or primary amenorrhea (Turner syndrome), frequent miscarriages, infertility, multiple congenital anomalies, sex determination, and many others. A chromosomal microarray study (CMACB / Chromosomal Microarray, Congenital, Blood) is recommended as the first-tier test (rather than a...
congenital chromosome study) to detect clinically relevant gains or losses of chromosomal material for individuals with multiple anomalies not specific to well-delineated genetic syndromes, individuals with apparently nonsyndromic developmental delay or intellectual disability, and individuals with autism spectrum disorders. -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). - T lymphocytes that do not respond to mitogens used to stimulate T cells to undergo mitosis (rare) - Chromosomal mosaicism may be missed due to statistical sampling error (rare) - Subtle structural chromosome abnormalities can occasionally be missed

**Useful For:** Diagnosis of congenital chromosome abnormalities, including aneuploidy, structural abnormalities, and balanced rearrangements

**Interpretation:** When interpreting results, the following factors need to be considered: - Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. - A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). - Chromosomal mosaicism may be missed due to statistical sampling error (rare) - Subtle structural chromosome abnormalities can occasionally be missed

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
that a qualified professional in Medical Genetics communicate all abnormal results to the patient.

Reference Values:
An interpretive report will be provided.


Chromosome Analysis, Hematologic Disorders, Blood

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and monitoring of treatment of many hematologic disorders. Whenever possible, it is best to do chromosome studies for neoplastic hematologic disorders on bone marrow. Bone marrow studies are more sensitive and the chances of finding metaphases are about 95%, compared with only a 60% chance for blood studies. When it is not possible to collect bone marrow, chromosome studies on blood may be useful. When blood cells are cultured in a medium without mitogens, the observation of any chromosomally abnormal clone may be consistent with a neoplastic process. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions. Conventional chromosome studies of B-cell disorders are not always successful because B-lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B-cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia (CLL), and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival.

Useful For: Assisting in the classification and follow-up of certain malignant hematological disorders when bone marrow is not available

Interpretation: The presence of an abnormal clone usually indicates a malignant neoplastic process. The absence of an apparent abnormal clone in blood may result from a lack of circulating abnormal cells and not from an absence of disease. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality and, thus, not related to a malignant process. When this situation is suspected, follow-up with a medical genetics consultation is recommended.

Reference Values:
An interpretive report will be provided.


Chromosome Analysis, Hematologic Disorders, Bone Marrow

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a
malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia, t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia, and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes.

Conventional chromosome studies of B-cell disorders are not always successful because B lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia, and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival. See Diagnosis and Monitoring of Multiple Myeloma in Publications.

**Useful For:** Assisting in the diagnosis and classification of certain malignant hematological disorders
Evaluation of prognosis in patients with certain malignant hematologic disorders
Monitoring effects of treatment
Monitoring patients in remission

**Interpretation:** To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: -Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a FISH study option that could be performed.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**CHFXH 64922 Chromosome Analysis, Hematologic Disorders, Fixed Cells**

**Clinical Information:** Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia, t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia, and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes.

**Useful For:** Assisting in the diagnosis and classification of certain malignant hematological disorders Evaluating the prognosis of patients with certain malignant hematologic disorders Monitoring effects of treatment Monitoring patients in remission
Interpretation: To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: - Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. - The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. - On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. - On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a FISH study option that could be performed.

Reference Values:
An interpretative report will be provided.

Clinical References:

CHRLN 35309
Chromosome Analysis, Lymphoid Tissue

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and monitoring of treatment of many hematologic disorders. The observation of a chromosomally abnormal clone is consistent with a clonal neoplastic process. Certain chromosome abnormalities can help classify the type of lymphoma. For example, t(14;18)(q32;q21.3) involving the IGH and BCL2 genes is usually indicative of a follicular lymphoma. A translocation between MYC and IGH genes or a t(8;14)(q24.1;q32) are both associated with Burkitt lymphoma. Cytogenetic studies often can help distinguish between B-cell and T-cell disorders. Structural abnormalities involving breakpoints at any immunoglobulin locus is consistent with a B-cell disorder; structural abnormalities involving breakpoints at a T-cell receptor site are usually associated with a T-cell disorder.

Useful For: Assisting in the classification of certain cases of lymphoma

Interpretation: The observation of a chromosomally abnormal clone is evidence of a clonal neoplastic process. Certain chromosome abnormalities also may be associated with certain morphologic classifications. However, a normal karyotype does not eliminate the possibility of a neoplastic process. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended.

Reference Values:
An interpretative report will be provided.

Clinical References:

CRAT 35316
Chromosome Analysis, Rearrangement in Ataxia Telangiectasia, Blood

Clinical Information: Chromosomal instability syndromes are autosomal recessive disorders characterized by defects in DNA repair mechanisms or genetic instability. Patients with these disorders have an increased risk of developing malignant disorders. When blood from affected individuals is
cultured and chromosome analysis is performed, elevated rates of chromosomal rearrangements are observed. These disorders include ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS). An increased frequency of chromosome rearrangements, including involvement at 7p13, 7q34, 14q11.2, or 14q32, signals a positive result. NBS usually has a higher frequency of cells with chromosome rearrangements than AT and generally does not include the clinical features of ataxia or increased serum alpha-fetoprotein. A normal result does not rule out a diagnosis of AT, NBS, or other chromosome instability syndromes.

**Useful For:** Evaluating patients for chromosome instability syndromes, including ataxia telangiectasia and Nijmegen breakage syndrome

**Interpretation:** The pattern of chromosome breakage and the number of breaks are compared to a normal control and an interpretive report is provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**BLOOM 35317**

**Chromosome Analysis, Sister Chromatid Exchange (SCE) for Bloom Syndrome, Blood**

**Clinical Information:** Sister chromatid exchange analysis is appropriate in individuals with clinical features suggestive of Bloom syndrome. Bloom syndrome is a genetic disorder associated with various congenital defects and predisposition to acute leukemia, pulmonary fibrosis, and Hodgkin lymphomas. Carcinoma also is commonly seen in these patients. Approximately one-fourth to one-half of patients develop some type of cancer with a mean age of 25 years at onset. The severity and age of onset of cancer varies among patients. These patients often have prenatal or postnatal growth retardation, short stature, malar hypoplasia, telangiectatic erythema of the face and other regions, hypo- and hyperpigmentation, immune deficiencies, occasional mild mental retardation, infertility, and high-pitched voices. Bloom syndrome is an autosomal recessive disorder caused by mutations in the BLM gene located at 15q26.1. While multiple mutations have been detected, the use of molecular testing to diagnose Bloom syndrome is limited in many ethnic groups. Patients with Bloom syndrome demonstrate a high frequency of chromosome abnormalities when their cells are cultured. Thus, cytogenetic studies can be helpful to establish a diagnosis. Bloom syndrome results in 2 characteristic cytogenetic abnormalities. First, the cells are at increased risk for random breaks leading to fragments or exchanges between nonhomologous chromosomes. Second, cells in these patients have an increased frequency of sister chromatid exchanges (SCE: exchange of material between homologous chromosomes) of approximately 10-fold to 20-fold higher than average. This test is diagnostic for Bloom syndrome. This test cannot be used to identify heterozygote carriers for Bloom syndrome and is not appropriate as part of a prenatal screening panel. A normal result does not rule out the possibility of birth defects, such as those caused by chromosomal abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). The test does not rule out other numeric or structural abnormalities. If a constitutional chromosome abnormality is suspected, a separate conventional cytogenetic study, CHRCB / Chromosome Analysis, for Congenital Disorders, Blood should be requested.

**Useful For:** Establishing a diagnosis of Bloom syndrome

**Interpretation:** A frequency of sister chromatid exchange comparable to a control specimen and historical reference values will be reported as normal. A 10-fold or more increase in sister chromatid
exchange relative to a control specimen and historical reference values will be reported as abnormal. This is consistent with a diagnosis of Bloom syndrome.

Reference Values:
An interpretive report will be provided.


Chromosome Analysis, Skin Biopsy

Clinical Information: Chromosomal abnormalities cause a wide range of disorders associated with birth defects and congenital diseases. Usually, the abnormalities can be demonstrated in peripheral blood, which is readily available. Chromosome analysis on skin fibroblasts may be indicated when the results from peripheral blood are inconclusive or in clinical circumstances such as suspected cases of chromosome mosaicism, confirmation of new chromosome disorders, or some dermatological disorders. Subtle structural chromosomal anomalies can occasionally be missed. Chromosomal mosaicism may be missed due to statistical sampling error (rare).

Useful For: Diagnosis of mosaic congenital chromosome abnormalities, including mosaic aneuploidy and mosaic structural abnormalities. Subsequent chromosome analysis when results from peripheral blood are inconclusive.

Interpretation: When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values: An interpretive report will be provided.


Chromosome Analysis, Solid Tumors

Clinical Information: Most malignant neoplasms are associated with clonal genetic abnormalities and the observation of an abnormal cytogenetic clone is consistent with a neoplasm. In many instances, these abnormalities can be demonstrated by cytogenetic analysis. Some physicians now consider cytogenetic analysis a useful laboratory test to determine the neoplastic potential of solid tumors. For some tumors, cytogenetic analysis can help classify solid tumors. For example, an X;18 translocation has been specifically associated with synovial sarcoma, many alveolar rhabdomyosarcomas have an associated 2;13 translocation, and nearly every myxoid liposarcoma has a 12;16 translocation. A complete summary of the correlation between tumor histology and specific chromosome abnormalities is too extensive to summarize here. The reader is referred to the Mitelman Database of Chromosome Aberrations and
Gene Fusions in Cancer. 2014 Available at URL: http://cgap.nci.nih.gov/Chromosomes/Mitelman

**Useful For:** Assisting in the classification of malignant tumors associated with chromosomal abnormalities

**Interpretation:** The observation of a chromosomally abnormal clone is evidence of a clonal neoplastic process. Certain chromosome abnormalities may also be specifically associated with certain morphologic classifications. In many tumors, the cytogenetic interpretation may be complicated by the observation of numerous complex chromosome anomalies. Nevertheless, the presence of certain chromosome abnormalities within a complex karyotype may still aid in classifying the tumor. However, a normal karyotype does not eliminate the possibility of a neoplastic process. Additionally, FISH testing or other strategies may be more appropriate for certain tumor types. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CHSUM 81385**

**Chronic Hepatitis (Unknown Type)**

**Clinical Information:** Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products, eg, blood transfusion, sharing of needles by drug addicts. The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic, others develop chronic liver disease including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. The following algorithms are available in Special Instructions: -Testing Algorithm for the Screening and Diagnosis of Hepatitis C -Chronic Hepatitis C Treatment and Monitoring Algorithm: Interferon-Free Combination Therapy -Viral Hepatitis Serologic Profiles

**Useful For:** The diagnosis and evaluation of patients with symptoms of hepatitis with a duration >6 months Distinguishing between chronic hepatitis B and chronic hepatitis C

**Interpretation:** Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profile in Special Instructions. Chronic Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B viral infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Anti-hepatitis B core (anti-HBe) appears shortly after the onset of symptoms. The IgM subclass usually falls to undetectable levels within 6 months, and the IgG subclass may remain for many years. Hepatitis B surface antibody (anti-HBs) usually appears with the resolution of hepatitis B virus infection after the disappearance of HBsAg. If HBsAg and anti-HBc (total antibody) are positive and patient's condition warrants, consider testing for hepatitis Be antigen (HBeAg), anti-HBe, hepatitis B virus DNA (HBV-DNA) or anti-hepatitis D virus (anti-HDV), Chronic Hepatitis C Virus (HCV): Anti-HCV is almost always detectable by the late convalescent and chronic stage of infection. The serologic tests currently available do not differentiate between acute and chronic hepatitis C infections.
Reference Values:
HEPATITIS B SURFACE ANTIGEN
Negative

HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE
Hepatitis B Surface Antibody
Unvaccinated: negative
Vaccinated: positive
Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <5.0 mIU/mL
Vaccinated: ≥12.0 mIU/mL

HEPATITIS B CORE TOTAL ANTIBODIES
Negative

HEPATITIS C ANTIBODY
Negative

Interpretation depends on clinical setting.


CHSBP 9023

Chronic Hepatitis Profile (Type B)

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products, eg, blood transfusion, sharing of needles by drug addicts. The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic; others develop chronic liver disease including cirrhosis and hepatocellular carcinoma. See HBV Infection–Diagnostic Approach and Management Algorithm and Viral Hepatitis Serologic Profile in Special Instructions.

Useful For: Evaluating patients with suspected or confirmed chronic hepatitis B Monitoring hepatitis B viral infectivity

Interpretation: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B viral (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either chronic carrier state or chronic liver disease. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. The presence of hepatitis B envelope antigen (HBeAg) correlates with infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and the presence of viral DNA polymerase in serum. Hepatitis B envelope antibody (anti-HBe) positivity in a carrier is often associated with chronic asymptomatic infection. If the patient has a sudden exacerbation of disease, consider ordering hepatitis C virus antibody and hepatitis delta virus antibody (anti-HDV). If HBsAg converts to negative and patient's condition warrants, consider testing for anti-HBs. If HBsAg is positive, consider testing for anti-HDV. See HBV Infection–Diagnostic Approach and Management Algorithm and Viral Hepatitis Serologic Profile in
Special Instructions.

**Reference Values:**
HEPATITIS B SURFACE ANTIGEN
Negative

HEPATITIS Be ANTIGEN
Negative

HEPATITIS Be ANTIBODY Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.


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**CLLF 35266**

**Chronic Lymphocytic Leukemia (CLL), FISH**

**Clinical Information:** Chronic lymphocytic leukemia (CLL) is the most common leukemia in North America. The most common cytogenetic abnormalities in CLL involve chromosomes 6, 11, 12, 13, and 17. These are detected and quantified using the CLL FISH panel. Use of CpG-oligonucleotide mitogen will identify an abnormal CLL karyotype in at least 80% of cases. This mitogen is added to cultures when chromosome analysis is ordered and the reason for referral is a B-cell disorder (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow and CHRHB / Chromosome Analysis, Hematologic Disorders, Blood). This FISH test detects an abnormal clone in approximately 70% of patients with indolent disease and >80% of patients who require treatment. At least 5% of patients referred for CLL FISH testing have translocations involving the IGH locus; approximately 66% of these patients have translocations that result in fusion of IGH/CCND1, IGH/BCL2, or IGH/BCL3. Fusion of IGH and CCND1 is associated with t(11;14)(q13;q32), IGH and BCL2 with t(14;18)(q32;q21), and IGH and BCL3 with t(14;19)(q32;q13.3). Patients with t(11;14)(q13;q32) usually have the leukemic phase of mantle cell lymphoma. Patients with t(14;18) or t(14;19) may have an atypical form of B-CLL or the leukemic phase of a lymphoma. The prognostic associations for chromosome abnormalities detected by this FISH assay are, from best to worst: 13q-, normal, +12, 6q-, 11q-, and 17p-.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with chronic lymphocytic leukemia (CLL) Identifying and tracking known chromosome abnormalities in patients with CLL and tracking response to therapy Distinguishing patients with atypical CLL or other forms of lymphoma associated with translocations between IGH and BCL2, BCL3, MYC, or other partner genes

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:** An interpretive report will be provided.

CHUB
82822

**Chub Mackerel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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CSU
81980

**Chyluria Screen**

**Clinical Information:** Chyle is lymphatic fluid that contains emulsified fats (chylomicrons). Chyle in the urine (chyluria) is the result of obstruction of lymph flow and rupture of lymphatic vessels into the renal tubules. Chyluria, also called galacturia, imparts a milky appearance to urine.

**Useful For:** Diagnosis of chyluria (galacturia)

**Interpretation:** This assay provides information regarding the fat content in urine fluid. Urinary cholesterol and triglyceride values are normally <10 mg/dL. High triglycerides in urine may indicate...
chyluria.

**Reference Values:**
No lipoproteins present

**Clinical References:** Diamond E, Schapira HE: Chyluria-a review of the literature. Urology 1985;26:427-431

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**CHYM 82609**

**Chymopapain, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**FCHYS 57806**

**Chymotrypsin, Stool**

**Reference Values:**
2.3 ìg-51.4 U/g
Cinnamon IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Cinnamon, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Circulating Immune Complexes (CIC)

**Interpretation:** Circulating immune complexes (CICs) are detectable in a variety of systemic disorders such as rheumatological, autoimmune, allergic diseases; viral, bacterial infections and malignancies. Although detection of CICs is neither essential nor specific for any disease, anti-C1q assay is likely to provide information regarding disease activity in lupus nephritis.

**Reference Values:**
- **Negative:** <20 EU/mL
- **Borderline/Equivocal:** 20 â€“ 25 EU/mL
- **Positive:** >25 EU/mL

Circulating Tumor Cells (CTC) for Breast Cancer by CellSearch, Blood

**Clinical Information:** In patients with metastatic cancer, tumor cells may be present in the bloodstream (circulating tumor cells: CTCs). Studies suggest that the number of CTCs is associated with progression-free and overall survival in patients with metastatic breast cancer.(1,2) Serial testing for CTCs, in conjunction with other clinical methods for monitoring breast cancer, can assist physicians in the management of these patients.(3)

**Useful For:** Aids in monitoring patients with metastatic breast cancer

**Interpretation:** Results are reported as favorable or unfavorable. In patients with metastatic breast cancer, unfavorable results (> or =5 circulating tumor cells/7.5 mL of blood) are predictive of shorter progression-free survival and shorter overall survival.(1)

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Circulating Tumor Cells (CTC) for Colorectal Cancer by CellSearch, Blood

**Clinical Information:** According to the American Cancer Society, colorectal cancer claims approximately 50,000 lives each year, the vast majority of which are a result of metastatic disease. Although there are many options for the treatment of metastatic colorectal cancer, oncologists often have to wait several months before they can determine if a specific treatment is beneficial to the patient. The CellSearch System identifies and enumerates the number of circulating tumor cells (CTCs) in a blood specimen.(1) Studies suggest that the number of CTCs is associated with progression-free and overall survival in patients with metastatic colorectal cancer.(2,3)

**Useful For:** Aids in monitoring patients with metastatic colon cancer

**Interpretation:** Results are reported as favorable or unfavorable. In patients with metastatic colon cancer, the finding of > or =3 circulating tumor cells/7.5 mL of blood is predictive of shorter progression-free survival and overall survival.(2)
Reference Values:
An interpretive report will be provided.


CTCPC
Circulating Tumor Cells (CTC) for Prostate Cancer by CellSearch, Blood

Clinical Information: According to the American Cancer Society, prostate cancer claims approximately 28,000 lives each year, the vast majority of which are a result of metastatic disease. Although there are many options for the treatment of metastatic prostate cancer, oncologists often have to wait several months after initiation of treatment before they can determine if the treatment is beneficial to the patient. The CellSearch System identifies and enumerates the number of circulating tumor cells (CTCs) in a blood specimen.(1) Studies suggest that the number of CTCs is associated with progression-free and overall survival in patients with metastatic prostate cancer.(2,3)

Useful For: Aids in monitoring patients with metastatic prostate cancer

Interpretation: Results are reported as favorable or unfavorable. In patients with metastatic prostate cancer, the finding of > or =5 circulating tumor cells/7.5 mL of blood is predictive of shorter progression-free survival and overall survival.(2)

Reference Values:
An interpretive report will be provided.


CITAL
Citalopram, Serum

Clinical Information: Citalopram (Celexa) and S-citalopram (escitalopram, Lexapro) are approved for treatment of depression. Celexa is a racemic mixture containing equal amounts of R- and S-enantiomer. Metabolites of citalopram (N-desmethylcitalopram) are less active than citalopram and do not accumulate in serum to clinically significant concentration. Citalopram metabolism is carried out by cytochrome P450 (CYP) 2C19 and 3A4-5. CYP 2D6 may play a minor role in citalopram metabolism. Citalopram is known to reduce CYP 2D6 activity. Citalopram clearance is significantly affected by reduced hepatic function, but only slightly by reduced renal function. A typical Celexa dose administered to an adult is 40-mg per day. A typical Lexapro dose is 20-mg per day. Citalopram is 80% protein bound, and the apparent volume of distribution is 12 L/Kg. Bioavailability is 80% and protein binding is 56% for either form of the drug. Time to peak serum concentration is 4 hours, and the elimination half-life is 35 hours. Half-life is increased in the elderly. Dosage reductions may be necessary for patients who are elderly or have reduced hepatic function.

Useful For: Monitoring citalopram therapy Identifying noncompliance, although regular blood level monitoring is not indicated in most patients Identifying states of altered drug metabolism when used in
conjunction with CYP2C19 and CYP3A4-5 genotyping

**Interpretation:** Steady-state serum concentrations associated with optimal response to citalopram are in the range of 50 to 100 ng/mL when the patient is administered the R,S-enantiomeric mixture (Celexa). The most common toxicities associated with excessive serum concentration are fatigue, impotence, insomnia, and anticholinergic effects. The toxic range for citalopram is >220 ng/mL.

**Reference Values:**
50-110 ng/mL

**Clinical References:**

**CITR**

**Citrate Excretion, 24 Hour, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate promotes kidney stone formation and growth, and is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

**Interpretation:** Any value less than the mean for 24 hours represents a potential risk for kidney stone formation and growth. Patients with low urinary citrate, and new or growing stone formation, may benefit from adjustments in therapy known to increase urinary citrate excretion. (See Clinical Information) Very low levels (<150 mg/24 hours) suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis).

**Reference Values:**
0-19 years: not established
20 years: 150-1,191 mg/24 hours
21 years: 157-1,191 mg/24 hours
22 years: 164-1,191 mg/24 hours
23 years: 171-1,191 mg/24 hours
24 years: 178-1,191 mg/24 hours
25 years: 186-1,191 mg/24 hours
26 years: 193-1,191 mg/24 hours
27 years: 200-1,191 mg/24 hours
28 years: 207-1,191 mg/24 hours
29 years: 214-1,191 mg/24 hours
30 years: 221-1,191 mg/24 hours
31 years: 228-1,191 mg/24 hours
32 years: 235-1,191 mg/24 hours
33 years: 242-1,191 mg/24 hours
34 years: 250-1,191 mg/24 hours
35 years: 257-1,191 mg/24 hours
36 years: 264-1,191 mg/24 hours
37 years: 271-1,191 mg/24 hours
38 years: 278-1,191 mg/24 hours
39 years: 285-1,191 mg/24 hours
40 years: 292-1,191 mg/24 hours
41 years: 299-1,191 mg/24 hours
42 years: 306-1,191 mg/24 hours
43 years: 314-1,191 mg/24 hours
44 years: 321-1,191 mg/24 hours
45 years: 328-1,191 mg/24 hours
46 years: 335-1,191 mg/24 hours
47 years: 342-1,191 mg/24 hours
48 years: 349-1,191 mg/24 hours
49 years: 356-1,191 mg/24 hours
50 years: 363-1,191 mg/24 hours
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54 years: 392-1,191 mg/24 hours
55 years: 399-1,191 mg/24 hours
56 years: 406-1,191 mg/24 hours
57 years: 413-1,191 mg/24 hours
58 years: 420-1,191 mg/24 hours
59 years: 427-1,191 mg/24 hours
60 years: 434-1,191 mg/24 hours
>60 years: not established


Citrate Excretion, Pediatric, Random, Urine

Clinical Information: Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition which lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

Useful For: Diagnosing risk factors for patients with calcium kidney stones. Monitoring results of therapy in patients with calcium stones or renal tubular acidosis. A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children. Therefore, this random test is offered for children <16 years old.

Interpretation: A low value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate, and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low levels suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis). For children ages 5 to 18, a ratio of <0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

Reference Values:
No established reference values


Citric Acid, Serum

Reference Values:
1.7 â€“ 3.7 mg/dL
**CKP53 Protocol, Blood**

**Reference Values:**
Only orderable as a reflex. For further information see test P53CA / Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9.

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**Cladosporium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**CLL Monitoring, MRD Detection, Blood**

**Clinical Information:** Chronic lymphocytic leukemia (CLL) is a low-grade, B-cell neoplasm that is the most common leukemia detected in the western world. It is a disease primarily of adults and may present as a lymphocytosis, be detected as part of a lymphadenopathy evaluation, or be found incidentally in an otherwise asymptomatic patient. The diagnosis of CLL is based on a combination of morphologic features showing primarily small lymphoid cells with coarse chromatin and scant cytoplasm and an immunophenotype of clonal B-cells with dim immunoglobulin, dim CD20, and coexpression of CD5 and CD23. New therapeutic approaches in CLL have been increasingly successful with some patients showing no or only very minimal residual disease (MRD) in their peripheral blood or bone marrow specimens following a therapeutic course. Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD is an important prognostic indicator in these patients.

**Useful For:** Confirming the presence or absence of minimal residual disease in patients with known chronic lymphocytic leukemia who are either postchemotherapy or post-bone marrow transplantation

**Interpretation:** An interpretive report for presence or absence of minimal residual disease (MRD) for chronic lymphocytic leukemia (CLL) is provided. Individuals without CLL should not have detectable
clonal B cells in the peripheral blood or bone marrow. Patients who have detectable MRD by this assay are considered to have residual CLL disease.

**Reference Values:**
An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

**Clinical References:**

FCLBZ 57709  
**Clobazam, Serum/Plasma**  
**Reference Values:**  
Clobazam: 30 - 300 ng/mL  
Desmethylclobazam: 300 - 3000 ng/mL

FCLM 75080  
**Clomipramine (Anafranil) and Desmethylclomipramine**  
**Reference Values:**  
Clomipramine and Desmethylclomipramine combined total: 230 - 450 ng/mL

CLOM 80902  
**Clomipramine, Serum**  
**Clinical Information:** Clomipramine (chlorimipramine, Anafranil) is a tricyclic antidepressant drug used primarily to treat obsessive-compulsive disorder (OCD). Clomipramine is also used to treat panic disorder and treatment-resistant depression. Clomipramine preferentially blocks synaptic reuptake of serotonin; its pharmacologically active metabolite, norclomipramine (desmethylchlorimipramine) preferentially blocks synaptic reuptake of norepinephrine. Clomipramine undergoes significant first-pass hepatic metabolism (up to 50%) which probably explains the high degree of interindividual variability observed between administered dose and steady-state serum concentrations of the drug and its metabolite. The serum ratio of clomipramine to norclomipramine is typically 1:2-2.5. The elimination half-lives of clomipramine and norclomipramine are 19-37 hours and 54-77 hours, respectively. One to two weeks are required to achieve steady-state when a patient is started on clomipramine or following an alteration in the dose. Anticholinergic side effects (ie, dry mouth, excessive sweating, blurred vision, urinary retention, constipation) frequently accompany treatment. Other side effects may include tremor, nausea, orthostatic hypotension, dizziness, sexual dysfunction, and sleep disturbances. Signs and symptoms following overdose are similar to other tricyclic antidepressant drugs: cardiac toxicity (eg, tachycardia, arrhythmia, impaired conduction, congestive heart failure) is the major concern.

**Useful For:** Determining whether a poor therapeutic response is attributable to noncompliance  
Monitoring serum concentration of clomipramine and norclomipramine to assist in optimizing the administered dose

**Interpretation:** Studies investigating the relationship between serum concentrations of clomipramine and norclomipramine and therapeutic response have yielded conflicting results. However, the probability of therapeutic failure seems to increase if the sum of the clomipramine and norclomipramine serum concentrations is <230 ng/mL. Summed serum concentrations of clomipramine and norclomipramine which exceed 450 ng/mL seem to result in no additional enhancement in therapeutic response and may predispose the patient to greater risk of adverse side affects. A toxic range has not been well established at this time.

**Reference Values:**  
CLOMIPRAMINE AND NORCLOMIPRAMINE  
Therapeutic concentration: 230-450 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clonazepam and 7-Aminoclonazepam, Serum

**Clinical Information:** Clonazepam [5 (2-chlorophenyl)-2, 3-dihydro-7-nitro-1, 4-benzodiazepin-2-one] is a benzodiazepine that is useful alone or as an adjunct in the treatment of certain seizures. In addition, it may be useful in patients with panic disorder, and restless legs syndrome. Clonazepam has no definite antiseizure and antipanic mechanism of action, although it is believed to be related to its capacity to enhance gamma-aminobutyric acid (GABA) activity, which is the major inhibitory neurotransmitter in the central nervous system. It is able to suppress the spike and wave discharges in absence seizures and decrease the frequency, duration, amplitude and spread of discharge in minor motor seizures. Clonazepam is highly protein bound (approximately 85%). It is extensively metabolized by hepatic P450 CYP3A, to inactive metabolites, and has a half-life of 30 to 40 hours.

**Useful For:** Assessing compliance Monitoring for appropriate therapeutic level Assessing toxicity

**Interpretation:** The therapeutic range varies depending on the indication. Some individuals may respond well outside of these ranges, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. The possibility of toxicity is increased when levels exceed 100 ng/mL. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

Clonazepam
- Anticonvulsant: 20-70 ng/mL
- Anxiolytic: 4-80 ng/mL

Some individuals may show therapeutic response outside of these ranges, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation.

- Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


Clonazepam, Urine as metabolite

**Reference Values:**

Units: ng/mL

Clonididine (Catapres)

**Reference Values:**

Reference Range: 1.00 - 2.00 ng/mL

Sedation has been associated with serum clonidine concentrations greater than 1.5 ng/mL

- Toxic concentration has not been established.

Clostridium difficile Culture

**Clinical Information:** Clostridium difficile can cause diarrhea, and may cause pseudomembranous colitis. Overgrowth of toxin-producing Clostridium difficile in the colon leads to the production of toxins.
A and/or B by the organism, and consequent diarrhea. Clostridium difficile infection should be suspected in patients with symptoms of diarrhea with risk factors such as current or recent use of antibiotics, history of Clostridium difficile infection, current or recent hospitalization or placement in a nursing home or long-term care facility, age >65 years, gastric acid suppression, etc. Clostridium difficile infection is the most common cause of diarrhea in hospitalized patients and may lead to serious complications, including sepsis, bowel perforation, and increased overall mortality (especially in elderly patients). The incidence of Clostridium difficile infection has risen in the community and in healthcare settings. While culture is not the preferred means to diagnose Clostridium difficile-associated diarrhea, culture for Clostridium difficile provides an isolate suitable for antimicrobial susceptibility testing. Note that this test does not differentiate between toxin-producing and nontoxigenic strains of Clostridium difficile.

**Useful For:** Clostridium difficile culture provides an isolate suitable for antimicrobial susceptibility testing.

**Interpretation:** A positive result indicates the presence of viable Clostridium difficile in stool. A positive culture may be found with asymptomatic Clostridium difficile colonization with a toxin-producing or non-toxin-producing strain, or with Clostridium difficile-associated diarrhea. A negative result indicates the absence of Clostridium difficile growth in culture. Isolation of Clostridium difficile does not differentiate between toxin-producing and non-toxin-producing strains.

**Reference Values:**
No growth after 1 day of incubation.

**Clinical References:** Cohen SH, Gerding DN, Johnson S, et al: Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31(5):431-455

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**Clostridium difficile Toxin, Molecular Detection, PCR, Feces**

**Clinical Information:** Clostridium difficile is the cause of Clostridium difficile-associated diarrhea (CDAD), an antibiotic-associated diarrhea, and pseudomembranous colitis (PMC). In these disorders bacterial overgrowth of Clostridium difficile develops in the colon, typically as a consequence of antibiotic usage. Clindamycin and broad-spectrum cephalosporins have been most frequently associated with CDAD and PMC, but almost all antimicrobials may be responsible. Disease is related to production of toxin A and/or B. Treatment typically involves withdrawal of the associated antimicrobials and, if symptoms persist, orally administered and intraluminally active metronidazole, vancomycin, or fidaxomicin. Intravenous metronidazole may be used if an oral agent cannot be administered. In recent years, a more severe form of CDAD with increased morbidity and mortality has been recognized as being caused by an epidemic toxin-hyperproducing strain of Clostridium difficile (NAP1 strain). Many toxin-hyperproducing isolates also contain the binary toxin gene and are resistant quinolones. This test does not differentiate between toxin-hyperproducing and nontoxin-hyperproducing strains. Traditionally, diagnosis relied upon 1) clinical and epidemiologic features, 2) culture (which is labor intensive and time consuming), 3) cytotoxicity assays, which are labor intensive and time consuming, and 4) toxin detection immunoassays (which are insensitive). The described PCR assay detects the regulatory gene (tcdC) responsible for production of toxins A and B. This test is used for rapid diagnosis of CDAD and PMC enabling prompt treatment that may reduce hospital stays for inpatients with CDAD.

**Useful For:** Sensitive, specific, and rapid diagnosis of Clostridium difficile-associated diarrhea and pseudomembranous colitis

**Interpretation:** A positive PCR result for the presence of the gene regulating toxin production (tcdC) indicates the presence of Clostridium difficile and toxin A and/or B. A negative result indicates the absence of detectable Clostridium difficile tcdC DNA in the specimen, but does not rule-out Clostridium difficile infection. False-negative results may occur due to inhibition of PCR, sequence variability underlying the primers or probes, or the presence of Clostridium difficile in quantities less than the limit of detection of the assay.

**Reference Values:**

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clove, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>(\geq100)</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


CLOV

82490
Clozapine, Serum

Clinical Information: Clozapine (Clozaril), a tricyclic dibenzodiazepine, is used for the symptomatic management of psychotic disorders and is considered an atypical antipsychotic drug. It is currently used primarily for the treatment of patients with schizophrenia or schizoaffective disorders who are at risk for recurrent suicidal behavior and who have encountered nonresponse or adverse, intolerable extra-pyramidal side effects with more classical antipsychotics (chlorpromazine, haloperidol). Although clozapine was developed about 30 years ago and the initial results were promising, the development of several fatal cases of agranulocytosis resulted in the discontinued use of this agent. Seizures, an increased risk of fatal myocarditis, and orthostatic hypotension have also been associated with the use of clozapine. The use of clozapine has regained interest for several reasons. Patients who did not respond to treatment with other antipsychotics improved when clozapine was administered. Also, the agranulocytosis that occurs in approximately 1% to 2% of patients can be controlled with close hematologic monitoring. However, because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should only be used in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse reactions from those drugs. Treatment is usually started with dosages of 25 to 75 mg/day with a gradual increase to reach a final dose of 300 to 450 mg/day within approximately 2 weeks of the initiation of treatment. Once the desired effect is achieved, the dose may be gradually decreased to keep the patient on the lowest possible effective dose. Patients being treated with clozapine should be closely monitored during treatment for adverse reactions. Treatment must include monitoring of white blood cell count and absolute neutrophil count. Clozapine treatment should be discontinued in patients failing to show an acceptable clinical response. In addition, in patients exhibiting beneficial clinical responses, the need for continuing treatment should be periodically reevaluated. Clozapine is metabolized to desmethylated and N-oxide derivatives. The desmethyl metabolite (norclozapine) has only limited activity, and N-oxide metabolite is inactive.

Useful For: Monitoring patient compliance An aid to achieving desired plasma levels

Interpretation: The effectiveness of clozapine treatment should be based on clinical response and treatment should be discontinued in patients failing to show an acceptable clinical response.

Reference Values:
CLOZAPINE
Therapeutic range: >350 ng/mL

CLOZAPINE + NORCLOZAPINE
Therapeutic range: >450 ng/mL

Clinical References:

CMV by PCR

Reference Values:
Not detected = Negative, no virus detected
Detected = Positive, virus detected
<1000 copies/mL = Positive. Virus detected below 1000 copies/mL
1000 copies/mL to 1,000,000 copies/mL = Positive
This test employs real-time PCR amplification of a Cytomegalovirus-specific conserved genetic target. A positive result should be coupled with clinical indicators for diagnosis. A "Not detected" result for this assay does not exclude Cytomegalovirus involvement in a disease process.

Coagulation Factor II Activity Assay, Plasma

**Clinical Information:** Factor II (prothrombin) is a vitamin K-dependent serine protease synthesized in liver. It participates in the final common pathway of coagulation, as the substrate for the prothrombinase enzyme complex. Prothrombin is the precursor of thrombin (IIa) which converts fibrinogen to fibrin. Plasma biological half-life is about 3 days. Deficiency of factor II may cause prolonged prothrombin time and activated partial thromboplastin time. Deficiency may result in a bleeding diathesis.

**Useful For:** Diagnosing a congenital deficiency (rare) of coagulation factor II Evaluating acquired deficiencies associated with liver disease or vitamin K deficiency, oral anticoagulant therapy, and antibody-induced deficiencies (eg, in association with lupus-like anticoagulant) Determining warfarin treatment stabilization in patients with nonspecific inhibitors (ie, lupus anticoagulant) Determining degree of anticoagulation with warfarin to correlate with level of protein S Investigation of prolonged prothrombin time or activated partial thromboplastin time

**Interpretation:** Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor II activity. Homozygotes generally have levels of <25% Heterozygotes generally have levels of <50% Normal newborn infants may have levels of 25% to 50%

**Reference Values:**

Adults: 75-145%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

Coagulation Factor II Inhibitor Screen, Plasma

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to factor II

**Interpretation:** Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

FACTOR II ACTIVITY ASSAY

Adults: 75-145%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.
FACTOR II INHIBITOR SCREEN
Negative


Coagulation Factor IX Activity Assay, Plasma
Clinical Information: Factor IX is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital deficiency inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) characterized by hemarthroses, deep tissue bleeding, excessive bleeding with trauma and ecchymoses. Acquired deficiency associated with liver disease, vitamin K deficiency, warfarin therapy and inhibitors (rare).

Useful For: Diagnosing deficiencies, particularly hemophilia B (Christmas disease) Assessing the impact of liver disease on hemostasis Investigation of a prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is more common than congenital. Mild hemophilia B: 5% to 50% Moderate hemophilia B: 1% to 5% Severe hemophilia B: <1%

Reference Values:
Adults: 65-140% Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which may not reach adult levels for > or =180 days postnatal.*
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


Coagulation Factor V Activity Assay, Plasma
Clinical Information: Factor V is a vitamin K-independent protein synthesized in the liver and in other tissues (endothelium, megakaryocytes/platelets). In its thrombin-activated form (factor Va), it serves as an essential cofactor in the prothrombinase enzyme complex which converts prothrombin to thrombin (the prothrombinase complex consists of the enzyme, activated factor X, factor Va cofactor, a phospholipid surface, and calcium). Deficiency of factor V may cause prolonged prothrombin time and activated partial thromboplastin time. Deficiency may result in a bleeding diathesis. Plasma biological half-life varies from 12 to 36 hours. Platelets contain 20% to 25% of the factor V in blood. Factor V (also known as labile factor) is highly susceptible to proteolytic inactivation, with the potential for spuriously decreased assay results.

Useful For: Diagnosing congenital deficiencies (rare) of coagulation factor V Evaluating acquired deficiencies associated with liver disease, factor V inhibitors, myeloproliferative disorders, and intravascular coagulation and fibrinolysis Investigation of prolonged prothrombin time or activated partial thromboplastin time

Interpretation: See Cautions Acquired deficiencies are much more common than congenital (see Useful For). Congenitally deficient homozygotes generally have levels < or =10% to 20%. Congenitally deficient heterozygotes generally have levels < or =50%. Congenital deficiency may occur in combined association with factor VIII deficiency.
Reference Values:
Adults: 70-165%
Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =30% to 35%) which reach adult levels within 21 days postnatal. Healthy premature infants (30-36 weeks gestation) may have borderline low or mildly decreased levels.*
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


Coagulation Factor V Inhibitor Screen, Plasma
Clinical Information: Factor V inhibitors can occur in patients with congenital factor V deficiency after transfusion of fresh frozen plasma, however, more commonly, they occur spontaneously in previously healthy older patients who have no underlying diseases. Topical bovine thrombin or fibrin glue, which contain bovine thrombin and factor V, are commonly used in surgery for topical hemostasis, can result in development of anti-bovine thrombin/factor V inhibitors that cross-react with human thrombin and factor V. Other associations include antibiotics, transfusions and malignancies.

Useful For: Detection and quantitation of inhibitors against coagulation factor V

Interpretation: Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR V ACTIVITY ASSAY
Adults: 75-165%
Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =30-35%) which reach adult levels within 21 days postnatal.*
Healthy premature infants (30-36 weeks gestation) may have borderline low or mildly decreased levels.*
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

FACTOR V INHIBITOR SCREEN
Negative


Coagulation Factor VII Activity Assay, Plasma
Clinical Information: Factor VII is a vitamin K-dependent serine protease synthesized in the liver. It is a component of the extrinsic coagulation scheme, measured by the prothrombin time. Plasma biological half-life is about 3 to 6 hours. Deficiency may result in a bleeding diathesis.

Useful For: Diagnosing congenital deficiency of coagulation factor VII Evaluating acquired deficiencies associated with liver disease, oral anticoagulant therapy, and vitamin K deficiency Determining degree of anticoagulation with warfarin to correlate with level of protein C Investigation of a prolonged prothrombin time

Interpretation: Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor VII activity. Heterozygotes generally have levels of < or =50%. Homozygotes have levels usually
<20%. Newborn infants usually have levels > or =25%.

Reference Values:
Adults: 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


F7IS 7809

Coagulation Factor VII Inhibitor Screen, Plasma

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Detection and quantitation of inhibitor to coagulation factor VII

Interpretation: Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR VII ACTIVITY ASSAY
Adults: 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

FACTOR VII INHIBITOR SCREEN
Negative


F8A 9070

Coagulation Factor VIII Activity Assay, Plasma

Clinical Information: Factor VIII is synthesized in the liver, and perhaps in other tissues. It is a coagulation cofactor which circulates bound to von Willebrand factor and is part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours). Congenital factor VIII decrease is the cause of hemophilia A which has an incidence of 1 in 10,000 and is inherited in a recessive sex-linked manner on the X chromosome. Severe deficiency (<1%) characteristically demonstrates as hemarthrosis, deep-tissue bleeding, excessive bleeding with trauma and ecchymoses. Factor VIII may be decreased in von Willebrand disease. Acquired deficiency states also occur. Antibodies specific for factor VIII are the most commonly occurring specific inhibitors of coagulation factors and can produce serious bleeding disorders (acquired hemophilia). Factor VIII is highly susceptible to proteolytic inactivation, with the potential for spuriously decreased assay results.
Useful For: Diagnosing hemophilia A. Diagnosing von Willebrand disease when measured with the von Willebrand factor (VWF) antigen and VWF activity. Diagnosing acquired deficiency states. Investigation of prolonged activated partial thromboplastin time.

Interpretation: See Cautions. Mild hemophilia A: 5% to 50%. Moderate hemophilia A: 1% to 5%. Severe hemophilia A: <1%. Congenital deficiency may also occur in combined association with factor V deficiency. Liver disease usually causes an increase of factor VIII activity. Acquired deficiencies of factor VIII have been associated with myeloproliferative or lymphoproliferative disorders (acquired von Willebrand disease; VWD), inhibitors of factor VIII (autoantibodies, post-partum conditions, etc.), and intravascular coagulation and fibrinolysis. May be decreased with von Willebrand factor in VWD.

Reference Values:
- Adults: 55-200%.
- Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

Clinical References:

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Coagulation Factor X Activity Assay, Plasma

Clinical Information: Factor X is a vitamin K-dependent serine protease that is synthesized in the liver. Its biological half-life is 24 to 48 hours. Factor X participates in both intrinsic and extrinsic pathways of coagulation (final common pathway) by serving as the enzyme (factor Xa) in the prothrombinase complex. Congenital factor X deficiency is rare. Acquired deficiency associated with liver disease, warfarin therapy, vitamin K deficiency, systemic amyloidosis and inhibitors (rare). Deficiency may cause prolonged prothrombin time and activated partial thromboplastin time.

Useful For: Diagnosing deficiency of coagulation factor X, congenital or acquired. Evaluating hemostatic function in liver disease. Investigation of prolonged prothrombin time or activated partial thromboplastin time.

Interpretation: Acquired deficiency more common than congenital. Homozygotes: <25%. Heterozygotes: 25% to 50%.

Reference Values:
- Adults: 70-150%.
- Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

Clinical References:
**Clinical Information:** The antithrombotic effect of oral vitamin K antagonists (e.g., warfarin) is mediated by reduction in the plasma activity of vitamin K-dependent procoagulant factors II (prothrombin) and X. The intensity of oral anticoagulation therapy with vitamin K antagonists must be monitored and adjusted to a narrow therapeutic range; undermedicating increases the risk of thrombosis, while overmedicating increases the risk of bleeding. Such therapy typically is monitored with the prothrombin time/international normalized ratio (INR) system. Lupus anticoagulants (LAC) are autoantibodies that interfere with phospholipid-dependent clotting tests and most commonly cause prolongation of the activated partial thromboplastin time (APTT). LAC can be associated with a prothrombotic disorder termed the antiphospholipid syndrome. LAC occasionally may cause prolongation of the baseline prothrombin time, rendering the INR system inaccurate for monitoring the intensity of oral anticoagulant therapy. LAC-induced prolongation of the prothrombin time is most commonly seen with recombinant human tissue factor thromboplastins (i.e., prothrombin time reagents) with a low international sensitivity index (ISI) such as Innovin (ISI = 1.0). The chromogenic factor X activity is an alternative assay for monitoring oral anticoagulant therapy. This assay is unaffected by LAC because the assay end point is not a phospholipid-dependent clotting time. Argatroban is a parenteral direct thrombin inhibitor that is approved for treatment of heparin-induced thrombocytopenia (HIT), an antibody-mediated prothrombotic disorder. Argatroban therapy prolongs the prothrombin time, which also renders the INR inaccurate for monitoring the warfarin effect while transitioning from Argatroban to oral anticoagulant therapy. The chromogenic coagulation factor X activity assay may be used as an alternative to the INR for monitoring and adjusting the warfarin dose during this transition.

**Useful For:** Monitoring oral anticoagulant therapy, especially in patients whose plasma contains lupus anticoagulants and in patients receiving the drug Argatroban

**Interpretation:** A chromogenic factor X activity of approximately 20% to 35% corresponds to the usual warfarin therapeutic INR range (i.e., INR = 2.0-3.0).

**Reference Values:**
60-140%


**F10IS 7811**

**Coagulation Factor X Inhibitor Screen, Plasma**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor X

**Interpretation:** Normally, there is no inhibitor, i.e., negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**
FACTOR X ACTIVITY ASSAY
Adults: 70-150%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

FACTOR X INHIBITOR SCREEN
Negative

**Clinical References:** 1. Feinstein DI: Acquired inhibitors of blood coagulation. In Hematology:
Coagulation Factor XI Activity Assay, Plasma

**Clinical Information:** Factor XI is synthesized in the liver. Its biological half-life is 60 to 80 hours. Factor XI is a component of intrinsic coagulation pathway which, when activated, activates factor IX to IXa. Factor XI deficiency may cause prolonged partial thromboplastin time. Deficiency associated with mild bleeding diathesis, but there is poor correlation between activity level and clinical bleeding. A relatively high incidence of congenital deficiency occurs among Ashkenazi Jewish descent (hemophilia C).

**Useful For:** Diagnosing deficiency of coagulation factor XI Investigation of prolonged activated partial thromboplastin time

**Interpretation:** Acquired deficiency is associated with liver disease and rarely inhibitors. Homozygotes: <20% Heterozygotes: 20% to 60%

**Reference Values:**
Adults: 55-150%
- Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**

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Coagulation Factor XI Inhibitor Screen, Plasma

**Clinical Information:** Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C), after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor XI

**Interpretation:** Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**
**FACTOR XI ACTIVITY ASSAY**
Adults: 55-150%
- Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR XI INHIBITOR SCREEN**
Negative

**Clinical References:**
Coagulation Factor XII Activity Assay, Plasma

Clinical Information: Factor XII is synthesized in the liver. Its biological half-life is 40 to 50 hours. Factor XII is a component of the contact activation system and is involved in both intrinsic pathway and fibrinolytic system Factor XII deficiency is often discovered when activated partial thromboplastin time is found to be unexpectedly long. The deficiency causes no known bleeding disorder. An association between severe factor XII deficiency and thrombosis risk has been proposed, but not proven.

Useful For: Diagnosing deficiency of coagulation factor XII Determining cause of prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is associated with liver disease, nephritic syndrome, and chronic granulocytic leukemia. Congenital homozygous deficiency: 20% Congenital heterozygous deficiency: 20% to 50%

Reference Values: Adults: 55-180%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15% to 20%) which may not reach adult levels for > or =180 days postnatal.*


Cobalt, 24 Hour, Urine

Clinical Information: Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt exposure Monitoring metallic prosthetic implant wear

Interpretation: Concentrations > or =2.0 mcg/specimen indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/specimen) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is >5 mcg/specimen, consistent with prosthesis wear. Urine concentrations >20 mcg/specimen in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values: 0.0-1.9 mcg/specimen

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Reference values apply to all ages.


Cobalt, Random, Urine

Clinical Information: Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt exposure Monitoring metallic prosthetic implant wear

Interpretation: Concentrations >=2.0 mcg/L indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/L) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is >5 mcg/L, consistent with prosthesis wear. Urine concentrations >20 mcg/L in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0.0-1.9 mcg/L

Reference values apply to all ages.


Cobalt, Serum

Clinical Information: Cobalt is rare but widely distributed in the environment, used in the
manufacture of hard alloys with high melting points and resistance to oxidation; cobalt alloys are used in manufacture of some artificial joint prosthesis devices. Cobalt salts are used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is an essential cofactor in vitamin B12 metabolism. Cobalt deficiency has not been reported in humans. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Serum cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt toxicity Monitoring metallic prosthetic implant wear

Interpretation: Concentrations &ge;1.0 ng/mL indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. If cobalt is ingested, concentrations &gt; 5 ng/mL suggest major exposure and likely toxicity. If cobalt exposure is due to orthopedic implant wear, there are no large case number reports associating high circulating serum cobalt with toxicity. There are no Occupational Health and Safety Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (4-10 ng/mL) in serum cobalt is likely to be associated with a prosthetic device in good condition. Serum concentrations &gt;10 ng/mL in a patient with cobalt-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0.0-0.9 ng/mL
&lt;10 ng/mL (MoM implant)

Clinical References:

COBCU 60353 Cobalt/Creatinine Ratio, Random, Urine

Clinical Information: Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in...
patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting cobalt exposure Monitoring metallic prosthetic implant wear

**Interpretation:** Concentrations \( \geq 2.0 \text{ mcg/g creatinine} \) indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/g creatinine) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is >5 mcg/g creatinine, consistent with prosthesis wear. Urine concentrations >20 mcg/g creatinine in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**

0.0-1.9 mcg/g Creatinine

Reference values apply to all ages.

**Clinical References:**


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**FCABL 57764**

**Cocaine Analysis-Whole Blood**

**Reference Values:**

This specimen was screened by Immunoassay. Any positive result is confirmed by gas chromatography with mass spectrometry (GC/MS). The following threshold concentrations are used for this analysis:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening Threshold</th>
<th>Confirmation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine metabolites</td>
<td>25 ng/mL</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoylecgonine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**COKMX 62720**

**Cocaine and Metabolite Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and to a lesser extent in India, Africa, and Java.(1) Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history and is rooted into the drug culture in the United States,(2) and is one of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly ethanol, and the simultaneous use of both drugs can be determined by the presence of the unique metabolite cocaethylene.(4) Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid.
Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.\(^{(7)}\) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.\(^{(8)}\) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.\(^{(7)}\) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at \(>\ or = 50\) ng/g is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

**Negative**

Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**

- Cocaine by LC-MS/MS: 50 ng/g
- Benzoylecgonine by LC-MS/MS: 50 ng/g
- Cocaethylene by LC-MS/MS: 50 ng/g
- m-Hydroxybenzoylecgonine by LC-MS/MS: 50 ng/g

**Clinical References:**

with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Reports will specifically indicate the presence or absence of cocaine and benzoylecgonine. The presence of cocaine, or its major metabolite, benzoylecgonine, indicates use within the past 4 days. Cocaine has a 6-hour half-life, so it will be present in urine for 1 day after last use. Benzoylecgonine has a half-life of 12 hours, so it will be detected in urine up to 72 hours after last use. There is no correlation between concentration and pharmacologic or toxic effects.

**Reference Values:**
Negative
Positives are reported with a quantitative GC-MS result.

Cutoff concentrations:

**IMMUNOASSAY SCREEN**
<150 ng/mL

**COCAINE BY GC-MS**
<50 ng/mL

**BENZOYLECGONINE BY GC-MS**
<50 ng/mL

**Clinical References:**

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**COKEU** 9286

**Cocaine and Metabolite Confirmation, Urine**

**Clinical Information:** Cocaine is a drug of current health concern because of its proliferation among recreational drug abusers. Freebase and crack increase the potential for major cocaine toxicity. Cocaine use is declining across the nation according to the National Institute of Drug Abuse. Increasingly, laboratory results are disputed or there are medical/legal overtones. Therefore, physicians are finding an increased need to confirm positive results before informing or confronting the patients.

**Useful For:** Detecting and confirming drug abuse involving cocaine

**Interpretation:** Reports will specifically indicate the presence or absence of cocaine and benzoylecgonine. The presence of cocaine, or its major metabolite, benzoylecgonine, indicates use within the past 4 days. Cocaine has a 6-hour half-life, so it will be present in urine for 1 day after last use. Benzoylecgonine has a half-life of 12 hours, so it will be detected in urine up to 4 days after last use. There is no correlation between concentration and pharmacologic or toxic effects.

**Reference Values:**
Negative
Positives are reported with a quantitative GC-MS result.

Cutoff concentrations:

**COCAINE BY GC-MS**
<50 ng/mL

**BENZOYLECGONINE BY GC-MS**
<50 ng/mL

**Clinical References:**

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**Cocaine and Metabolites Confirmation, Meconium**

**Clinical Information:** Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and to a lesser extent in India, Africa, and Java. Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history and is rooted into the drug culture in the United States and is 1 of the most common illicit drugs of abuse. Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE). Cocaine is frequently used with other drugs, most commonly ethanol, and the simultaneous use of both drugs can be determined by the presence of the unique metabolite cocaethylene. Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage). The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth

**Interpretation:** The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at > or = 50 ng/g is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**
- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - Cocaine by LC-MS/MS: 50 ng/g
  - Benzoylecgonine by LC-MS/MS: 50 ng/g
  - Cocaethylene by LC-MS/MS: 50 ng/g
  - m-Hydroxybenzoylecgonine by LC-MS/MS: 50 ng/g

**Clinical References:**

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**Coccidioides Antibody with Reflex, Serum**

**Clinical Information:** Coccidioidomycosis (Valley fever, San Joaquin Valley fever, Desert Rheumatism) is caused by the dimorphic fungus Coccidioides immitis/posadasii, which is found in the southwestern United States and in Central and South America. It is acquired by inhalation of airborne Coccidioides arthroconidia. The majority of infections are subclinical. Among symptomatic patients, the majority will present acute flulike, pulmonary symptoms approximately 7 to 28 days post exposure, which
may include chest pain, cough, fever, malaise, and lymphadenopathy.(1) A rash often develops within a couple of days, followed by erythema nodosum or multiforme with accompanying arthralgia. A pulmonary coin-like lesion or nodule may develop months following infection and may be a source of infection if the patient becomes immunosuppressed in the future. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. Individuals at greater risk for dissemination include African-Americans, patients of Filipino descent, pregnant women, and immunocompromised patients.(2) Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: Screening for detection of antibodies to Coccidioides immitis/posadasii

Interpretation: A positive result is presumptive evidence that the patient was previously or is currently infected with Coccidioides immitis/posadasii. This specimen will be tested by complement fixation and immunodiffusion for confirmation. A negative result indicates the absence of antibodies to Coccidioides immitis/posadasii and is presumptive evidence that the patient has not been previously exposed to and is not infected with Coccidioides. However, a negative result does not preclude the diagnosis of coccidioidomycosis as the specimen may have been drawn before antibodies levels were detectable due to early acute infection or immunosuppression. If infection is suspected, another specimen should be drawn in 7 to 14 days and retested to look for seroconversion. This test is designed for the qualitative detection of both IgM- and IgG-class antibodies against antigens from Coccidioides. The report will not indicate which class of antibody is present.

Reference Values:
Negative


Coccidioides Antibody with Reflex, Spinal Fluid

Clinical Information: Coccidioidomycosis (Valley fever, San Joaquin Valley fever, Desert Rheumatism) is caused by the dimorphic fungus Coccidioides immitis/posadasii, which is found in the southwestern United States and in Central and South America. It is acquired by inhalation of airborne Coccidioides arthroconidia. The majority of infections are subclinical. Among symptomatic patients, the majority will present acute flulike, pulmonary symptoms approximately 7 to 28 days post exposure, which may include chest pain, cough, fever, malaise, and lymphadenopathy.(1) A rash often develops within a couple of days, followed by erythema nodosum or multiforme with accompanying arthralgia. A pulmonary coin lesion or nodule may develop months following infection and may be a source of infection if the patient becomes immunosuppressed in the future. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. Individuals at greater risk for dissemination include African-Americans, patients of Filipino descent, pregnant women and immunocompromised patients.(2) Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: An aid for the diagnosis of meningeal infection with Coccidioides immitis/posadasii

Interpretation: A positive result is presumptive evidence that the patient has a meningeal infection with Coccidioides immitis/posadasii. This specimen will be tested by complement fixation and immunodiffusion for confirmation. A negative result indicates the absence of antibodies to Coccidioides immitis/posadasii and is presumptive evidence that the patient has not been previously exposed to and is not infected with Coccidioides. However, a negative result does not preclude the diagnosis of coccidioidomycosis as the specimen may have been drawn before antibodies levels were detectable due to early acute infection or immunosuppression. If infection is suspected, another specimen should be drawn...
in 7 to 14 days and retested to look for seroconversion. This test is designed for the qualitative detection of both IgM- and IgG-class antibodies against antigens from Coccidioides. The report will not indicate which class of antibody is present.

Reference Values:
Negative

Clinical References:

Coccidioides Antibody, Complement Fixation and Immunodiffusion, Serum

Reference Values:
Negative

Coccidioides Antibody, Complement Fixation and Immunodiffusion, Spinal Fluid

Reference Values:
Negative

Coccidioides Antibody, Serum

Clinical Information: Coccidioidomycosis (Valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern United States, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis. Usually, it is a mild, self-limiting pulmonary infection, often leaving a coin-like lesion. Less commonly, chronic pneumonia may persist or progress to fibronodular, cavitary disease. A rash often develops within a day or 2, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgM precipitating antibodies.

Useful For: Diagnosing coccidioidomycosis Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Interpretation: Complement Fixation (CF): Titers of > or =1:2 may suggest active disease; however, titers may persist for months after infection has resolved. Increasing CF titers in serial specimens are diagnostic of active disease. Immunodiffusion (ID): The presence of IgM antibody may be detectable within 2 weeks after the onset of symptoms; however, antibody may be detected longer than 6 months after infection. The presence of IgG antibody parallels the CF antibody and may suggest an active or a recent asymptomatic infection with Coccidioides immitis; however, antibody may persist after the infection has resolved. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. Over 90% of primary symptomatic cases will be detected by combined ID and CF testing.

Reference Values:
COMPLEMENT FIXATION
Negative
If positive, results are titered.

**IMMUNODIFFUSION**
Negative
Results are reported as positive, negative, or equivocal.


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**Coccioidioides Antibody, Spinal Fluid**

**Clinical Information:** Coccioidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern United States, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccioides immitis. Usually, it is a mild, self-limiting pulmonary infection, often leaving a coin-like lesion. Less commonly, chronic pneumonia may persist or progress to fibronodular, cavitary disease. A rash often develops within 1 to 2 days, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccioidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges.

**Useful For:** Serologic testing for coccioidioidomycosis should be considered when patients exhibit symptoms of meningal infection and have lived or traveled in areas where Coccioides immitis is endemic. Any history of exposure to the organism or travel cannot be overemphasized when coccioidioidomycosis serologic tests are being considered.

**Interpretation:** Complement Fixation (CF): IgG antibody is detected by CF testing. Any CF titer in cerebrospinal fluid (CSF) should be considered significant. A positive complement fixation test in unconcentrated CSF is diagnostic of meningitis. Immunodiffusion (ID): IgM and IgG precipitins are rarely found in CSF. However, when present, they are diagnostic of meningitis (100% specific). Since the ID test is 100% specific, it is helpful in interpreting CF results. Early primary antibody (IgM) found in coccioidioidomycosis can be detected by the IgM-specific ID test. IgM precipitins may be detectable within 1 to 4 weeks after the onset of symptoms. The presence of IgG antibody parallels the CF antibody and indicates an active or a recent asymptomatic infection with Coccioides immitis. Both IgG and IgM antibodies are rarely detected 6 months after infection. However, in some patients having disseminated infection, both IgG and IgM antibodies may be present for several years. IgM and IgG precipitins are not prognostic. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. The sensitivity of serologic testing (CF and ID combined) for coccioidioidomycosis is >90% or primary symptomatic cases.

**Reference Values:**
COMPLEMENT FIXATION
Negative
If positive, results are titered.

IMMUNODIFFUSION
Negative
Results are reported as positive, negative, or equivocal.

and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America. The illness commonly manifests as a self-limited upper respiratory tract infection, but can also result in disseminated disease that may be refractory to treatment.(1) Clinical onset generally occurs 10 to 16 days following inhalation of coccidioidal spores (arthroconidia).(2) Disease progression may be rapid in previously healthy or immunosuppressed individuals. At present, the gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens. Culture is highly sensitive and, with the implementation of DNA probe assays for confirmatory testing of culture isolates, yields excellent specificity.(3) However, growth in culture may take up to several weeks. This often delays the diagnosis and treatment of infected individuals. In addition, the propagation of Coccidioides species in the clinical laboratory is a significant safety hazard to laboratory personnel, serving as an important cause of laboratory-acquired infections if the organism is not quickly identified and handled appropriately (ie, in a Biosafety Level 3 facility). Serological tests including immunodiffusion and complement fixation are widely used for the detection of antibody against Coccidioides. Serology for Coccidioides can be limited by delays in antibody development or nonspecificity due to cross-reactions with other fungi. In addition, immunodiffusion and complement fixation tests are highly labor intensive and are generally limited to reference laboratories. Molecular methods can identify Coccidioides species directly from clinical specimens, allowing for a more rapid diagnosis. Fungal culture should also be performed since the isolate may be needed for antifungal susceptibility testing.

**Useful For:** Rapid detection of Coccidioides DNA, preferred method An aid in diagnosing coccidioidomycosis

**Interpretation:** A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA.

**Reference Values:**
Not applicable

**Clinical References:**

**Coccidioides immitis/posadasii, Molecular Detection, PCR, Paraffin**

**Clinical Information:** Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America. The illness commonly manifests as a self-limited upper respiratory tract infection, but can also result in disseminated disease that may be refractory to treatment.(1) Clinical onset generally occurs 10 to 16 days following inhalation of coccidioidal spores (arthroconidia).(2) Disease progression may be rapid in previously healthy or immunosuppressed individuals. At present, the gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens. Culture is highly sensitive and, with the implementation of DNA probe assays for confirmatory testing of culture isolates, yields excellent specificity.(3) However, growth in culture may take up to several weeks. This often delays the diagnosis and treatment of infected individuals. Serological tests including immunodiffusion and complement fixation are widely used for the detection of antibody against Coccidioides. Serology for Coccidioides can be limited by delays in antibody development or nonspecificity due to cross-reactions with other fungi. In addition,
immunodiffusion and complement fixation tests are highly labor intensive and are generally limited to reference laboratories. Molecular methods can identify Coccidioides species directly from clinical specimens and should be used in conjunction with culture. For specimen types such as formalin-fixed, paraffin-embedded tissue, culture is not possible, but the molecular test may provide useful information.

**Useful For:** Rapid detection of Coccidioides DNA An aid in diagnosing coccidioidomycosis

**Interpretation:** A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA.

**Reference Values:**
Not applicable

**Clinical References:**

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### Cockatiel Droppings IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

### Cockatiel Feathers IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

### Cocklebur, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effect cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in old children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
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<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Cockroach, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
</table>

**FCOCN 57668**  
**Coconut IgG**  
**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200  
**Reference Values:**  
<2 mcg/mL  

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**CCNT 82739**  
**Coconut, IgE**  
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**  
Class IgE kU/L  Interpretation  
0  Negative  
1  0.35-0.69  Equivocal

**Codfish, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Coenzyme Q10, Reduced and Total, Plasma

Clinical Information: Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation, where it functions as an electron carrier and acts as an antioxidant. It is found in all cell membranes and is carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein (HDL), and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent not only on its concentration, but also on its reduction-oxidation (redox) status. Primary CoQ10 deficiency, although rare, is characterized by neurological symptoms (seizures, developmental delay, ataxia, etc) and muscle weakness. At least 5 different phenotypes of primary CoQ10 deficiency have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Childhood-onset cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Multi-systemic infant form (nystagmus, optic atrophy, sensorineuronal hearing loss, dystonia, rapidly progressing nephropathy) -Glomerulopathy -Myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies can improve mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including Parkinson disease, diabetes, and Alzheimer disease, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy; changes in CoQ10 may be relevant to statin-induced myalgia. The redox status of CoQ10 may be a useful early marker for the detection of oxidative LDL modification.

Useful For: Diagnosis of coenzyme Q10 (CoQ10) deficiency in mitochondrial disorders Monitoring patients receiving statin therapy Monitoring CoQ10 status during treatment of various degenerative conditions including Parkinson and Alzheimer disease

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
CoQ10 REDUCED
<18 years: 320-1,376 mcg/L
> or =18 years: 415-1,480 mcg/L

TOTAL CoQ10
<18 years: 320-1,558 mcg/L
> or =18 years: 433-1,532 mcg/L

% REDUCED CoQ10
<18 years: 93-100%
> or =18 years: 92-98%


Coenzyme Q10, Total, Plasma

**Clinical Information:** Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation, where it functions as an electron carrier and also acts as an antioxidant. It is found in all cell membranes and carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein (HDL), and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent not only on its concentration, but also on its reduction-oxidation (redox) status. Primary CoQ10 deficiency, although rare, is characterized by neurological symptoms (seizures, developmental delay, ataxia, etc) and muscle weakness. At least 5 different phenotypes have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Childhood-onset cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Glomerulopathy -Myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies improves mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including Parkinson disease, diabetes, and Alzheimer disease, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy; changes in CoQ10 may be relevant to statin-induced myalgia.

**Useful For:** Diagnosis of coenzyme Q10 (CoQ10) deficiency in mitochondrial disorders Monitoring patients receiving statin therapy Monitoring CoQ10 status during treatment of various degenerative conditions including Parkinson and Alzheimer disease This test can be used for hemolyzed specimens to provide accurate quantitation of total coenzyme Q10.

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated.

**Reference Values:**

<table>
<thead>
<tr>
<th>TOTAL CoQ10</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 years: 320-1,558 mcg/L</td>
</tr>
<tr>
<td>&gt; or =18 years: 433-1,532 mcg/L</td>
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</table>


**Clinical References:**


Coffee (Coffea spp) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.1 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 >=100 Very High Positive

**Reference Values:**

<0.35 kU/L

Cold Agglutinin Titer, Serum

Current as of July 8, 2016 11:28 am CDT
Clinical Information: The cold agglutinin titer test is to be used as a tool in the evaluation of suspected cold agglutinin syndrome. In this syndrome, cold agglutinins, usually IgM with anti-I specificity, attach to the patient's erythrocytes causing a variety of symptoms, from chronic anemia due to premature removal of the sensitized erythrocytes from circulation by hemolysis to acrocyanosis of the ears, fingers, or toes due to local blood stasis in the skin capillaries.

Useful For: Detection of cold agglutinins in patients with suspected cold agglutinin disease

Interpretation: Screen: -Negative (no cold agglutinin detected) -Positive (cold agglutinin detected, titer end point range will be reported) Titer: -Patients with cold agglutinin syndrome usually exhibit a titer value >1:512, with rare cases reportedly as low as 1:64. -Normal individuals often have low levels of cold agglutinins. The test is not a direct measure of clinical significance and must be used in conjunction with other in vitro and in vivo parameters.

Reference Values:
SCREEN
Negative

TITER
<1:64


Collagen Type II Antibodies

Interpretation: Anti-collagen II antibodies occur in 22% of patients with idiopathic SNHL, 30% of patients with sudden deafness and 20% of patients with Meniere’s disease. Anti-collagen II antibodies also occur in patients with relapsing polychondritis and in rheumatoid arthritis.

Reference Values:
Negative: <20 EU/mL
Borderline/Equivocal: 20-25 EU/mL
Positive: >25 EU/mL

Common Millet, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


**Common Reed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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5  50.0-99.9  Strongly positive
6  >or=100  Strongly positive Reference values apply to all ages.


Common Variable Immunodeficiency Confirmation Flow Panel

Clinical Information: Common variable immunodeficiency (CVID) is the most prevalent primary immunodeficiency with a prevalence of CVID of 1:25,000 to 1:50,000.(1) It has a bimodal presentation with a subset presenting in early childhood and a second set presenting between 15 and 40 years of age or even later. CVID is characterized by hypogammaglobulinemia usually involving most or all of the immunoglobulin (Ig) classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1) B cell numbers are usually normal, although a minority of patients (5%-10%) have very low B cell counts (<1% of peripheral blood leukocytes). It is reasonable to suspect a transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) defect in patients with low to absent IgA, low IgG, and low or normal IgM, along with splenomegaly, autoimmune cytopenias, autoimmune thyroiditis, and tonsillar hypertrophy. In TACI-deficient patients, there may be an increased risk for developing neoplasias such as non-Hodgkin lymphoma or other solid tumors. CD19 defects result in absence of B cells expressing CD19. When an alternative B-cell marker such as CD20 is used, however, B cells can be detected in the blood of these patients. Inducible T-cell costimulator (ICOS)-deficiency results in reduced class-switched memory B-cells. Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4/CD8 ratio (<1).(1) A subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T cell deficiency.(1) Patients with mutations in the TACI gene (see below) are particularly prone to developing autoimmune disease, including cytopenias as well as lymphoproliferative disease. The etiology of CVID is heterogeneous, but recently 4 genetic defects were described that are associated with the CVID phenotype. Specific mutations, all of which are expressed on B cells, have been implicated in the pathogenesis of CVID. These mutations encode for: -ICOS: inducible costimulator expressed on activated T cells(2) -TACI: transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor(3) -CD19(4) -BAFF-R: B-cell activating factor belonging to the tumor necrosis factor (TNF) receptor family(5) Of these, mutations of the gene that encodes TACI, TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B), probably account for about 10% to 15% of all CVID cases.(3) Patients with mutations in the TACI gene are particularly prone to developing autoimmune disease, including cytopenias, as well as lymphoproliferative disease. The other mutations each have been reported in only a handful of patients. The etiopathogenesis is still undefined in more than 75% to 80% of CVID patients. A BAFF-R defect should be suspected in patients with low to very low class switched and nonswitched memory B cells and very high numbers of transitional B cells (see IABC / B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood). Class switching is the process that allows B cells, which possess IgD and IgM on their cell surface as part of the antigen-binding complex, to produce IgA, IgE, or IgG antibodies. A TACI defect is suspected in patients with low IgA and low IgG with normal to low switched B cells, with autoimmune or lymphoproliferative manifestations or both, and normal B cell responses to mitogens.

Useful For: Screening for common variable immunodeficiency (CVID) Identifying defects in TACI and BAFF-R in patients presenting with clinical symptoms and other laboratory features consistent with CVID Evaluating B cell immune competence by assessing expression of BAFF-R and TACI proteins Useful for assessing BAFF-R and TACI protein expression and frequency of B cells bearing these receptors. TNFRSF13C (BAFF-R) and TNFRSF13B (TACI) gene mutations have been described in a small subset of patients with humoral immunodeficiencies classified as CVID. The majority of TNFRSF13B mutations preserve TACI protein expression and require genetic testing to identify pathogenic or potentially pathogenic mutations/variants.

Interpretation: BAFF-R is normally expressed on over 95% of B cells, while TACI is expressed on a
smaller subset of B cells (3%-70%) and some activated T cells. Expression on B cells increases with B cell activation. The lack of TACI or BAFF-R surface expression on B cells is suggestive of a potential common variable immunodeficiency (CVID)-associated defect, if other features of CVID are present. The majority of TACI mutations (>95%) preserve protein expression but abrogate protein function, hence the only way to conclusively establish a TACI mutational defect is to perform genetic testing (TACIF / Transmembrane Activator and CAML Interactor [TACI] Gene, Full Gene Analysis).

**Reference Values:**

- %CD19+TACI+: >3.4%
- %CD19+BAFF-R+: >90.2%

Reference values apply to all ages.

**Clinical References:**


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**C1Q, Serum**

**Clinical Information:** The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1, C2, C4) results in an inability to clear immune complexes. Inherited deficiency of C1 is rare. Like the more common C2 deficiency, C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus, polymyositis, glomerulonephritis, and Henoch-Schonlein purpura). Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton's and common variable hypogammaglobulinemia and severe combined immunodeficiency), and this is most likely due to increased catabolism. The measurement of C1q is an indicator of the amount of C1 present.

**Useful For:**

- Assessment of an undetectable total complement (CH50) level
- Diagnosing congenital C1 (first component of complement) deficiency
- Diagnosing acquired deficiency of C1 inhibitor

**Interpretation:** An undetectable C1q in the presence of an absent total complement (CH50) and normal C2, C3, and C4 suggests a congenital C1 (first component of complement) deficiency. A low C1q in combination with a low C1 inhibitor and low C4 suggests an acquired C1 inhibitor deficiency.

**Reference Values:**

12-22 mg/dL

**Clinical References:**


---

**C3, Serum**

**Clinical Information:** The complement system is an integral part of the immune defenses. The primary complement pathway consists of recognition (C1q, C1r, C1s), activation (C4, C2, C3), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. The complement system can be activated via immune complexes, and the alternative pathway (properdin pathway), which is activated primarily by foreign bodies such as microorganisms. C3 activation involves
Cleavage by C3 convertase into C3a and C3b. When immune complexes are not involved, the alternate method of complement activation initiates the reactant sequence at C3, bypassing C1, C4, and C2. Severe recurrent bacterial infections occur in patients with homozygous C3 deficiency and in those patients with low levels of C3 secondary to the absence of C3b activator. Decreased C3 may be associated with acute glomerulonephritis, membranoproliferative glomerulonephritis, immune complex disease, active systemic lupus erythematosus, septic shock, and end-stage liver disease.

**Useful For:** Assessing disease activity in systemic lupus erythematosus (SLE) Investigating an undetectable total complement (CH50) level

**Interpretation:** A decrease in C3 levels to the abnormal range is consistent with disease activation in systemic lupus erythematosus (SLE).

**Reference Values:**
75-175 mg/dL

**Clinical References:**

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**C4**

**Clinical Information:** The complement system is an integral part of the immune defenses. It can be activated via immune complexes (classic pathway) or by bacterial polysaccharides (alternative pathway). The classic complement pathway consists of recognition, (C1q, C1r, C1s), activation (C2, C3, C4), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. C4 is 1 of the activation proteins of the classic pathway. In the absence of C4, immune complexes will not be cleared by C3 activation peptides, but bacterial infections can still be defended via the alternative pathway. C4 may be decreased in systemic lupus erythematosus, early glomerulonephritis, immune complex disease, cryoglobulinemia, hereditary angioedema, and congenital C4 deficiency.

**Useful For:** Investigating an undetectable total complement (CH50) Confirming hereditary angioedema (with low C1 inhibitor) Assessing disease activity in systemic lupus erythematosus, proliferative glomerulonephritis, rheumatoid arthritis, and autoimmune hemolytic anemia

**Interpretation:** Decreased in acquired autoimmune disorders, in active phase of lupus erythematosus, and in rheumatoid arthritis An undetectable C4 level (with normal C3) suggests a congenital C4 deficiency Increased in patients with autoimmune hemolytic anemia

**Reference Values:**
14-40 mg/dL

**Clinical References:**

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**AH50**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: the classic pathway, the alternative (or properdin) pathway, and the lectin activation (or mannose-binding protein: MBP) pathway. The total hemolytic complement (CH50) assay (COM / Complement, Total, Serum) is the best screening assay for most complement abnormalities. It assesses the classical complement pathway including early components that activate the pathway in response to immune complexes, as well as the late components involved in the membrane attack complex. The CH50 assay will be abnormal if there are specific hereditary or acquired C1-C9 complement
component deficiencies or if there is consumption of complement due to immune (or autoimmune) complexes. The complement alternate pathway (AH50) assay is a screening test for complement abnormalities in the alternative pathway. The alternate pathway shares C3 and C5-C9 components, but has unique early complement components designated factors D, B, and P, as well as regulatory factors H and I. This pathway is activated by microbial polysaccharides and does not require immune complex formation. Patients with disseminated infections with pyogenic bacteria in the presence of a normal CH50 may have an absent AH50 due to hereditary or acquired deficiencies of the alternate pathway. Patients with deficiencies in the alternate pathway factors (D, B, P, H, and I) or late complement components (C3, C5-C9) are unusually susceptible to recurrent neisserial meningitis. The use of the CH50 and AH50 assays allow identification of the specific pathway abnormality. Unregulated alternative pathway can also result in disease. The majority of these diseases present with renal function impairment such as atypical hemolytic uremic syndrome (a-HUS), dense deposit disease (DDD), and C3 glomerulonephritis (C3GN).

**Useful For:** Investigation of suspected alternative pathway complement deficiency, atypical hemolytic uremic syndrome, C3 glomerulonephritis, dense-deposit disease

**Interpretation:** Absent complement alternate pathway (AH50) in the presence of a normal total hemolytic complement (CH50) suggests an alternate pathway component deficiency. Normal AH50 with absent CH50 suggests an early (C1, C2, C4) classic pathway deficiency. Absent AH50 and CH50 suggests a late (C3, C5, C6, C7, C8, C9) component deficiency or complement consumption. Absent AH50 and CH50 in the presence of a normal C3 and C4 suggests a late (C5, C6, C7, C8, C9) component deficiency.

**Reference Values:**
> or =46% normal

**Clinical References:**

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**Complement, Total, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: (1) the classic pathway, (2) the alternative (or properdin) pathway, and (3) the lectin activation (or mannan-binding protein) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1, C2, C3, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, and complement deficiency may be an etiologic factor in the development of autoimmune disease. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Undetectable complement levels are found in patients with specific component deficiency deficiencies. Decreased complement levels are found in infectious and autoimmune diseases due to fixation and consumption of complement.

**Useful For:** Detection of individuals with an ongoing immune process First-order screening test for congenital complement deficiencies

**Interpretation:** Low levels of total complement (total hemolytic complement CH50) may occur during infections, disease exacerbation in patients with systemic lupus erythematosus, and in patients with immune complex diseases such as glomerulonephritis. Undetectable levels suggest the possibility of a
complement component deficiency. Individual complement component assays are useful to identify the specific deficiency.

**Reference Values:**
> or =16 years: 30-75 U/mL

Reference values have not been established for patients that are <16 years of age.


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**Comprehensive Cardiomyopathy Multi-Gene Panel, Blood**

**Clinical Information:** The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other causes, such as structural abnormalities, systemic hypertension, or physiologic hypertrophy due to rigorous athletic training (athlete's heart). The incidence of HCM in the general population is approximately 1 in 500, and the hereditary form is most often caused by variants in genes encoding the components of the cardiac sarcomere. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can also cause life-threatening arrhythmias that increase the risk of sudden cardiac death. DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias or conduction system disease, or thromboembolic disease (stroke). The incidence of DCM is likely higher than originally reported due to subclinical phenotypes and underdiagnosis, with recent estimates suggesting that DCM affects approximately 1 in every 250 people. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. Arrhythmogenic right ventricular dysplasia (ARVD or AC) is characterized by breakdown of the myocardium and replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. Age of onset and severity are variable, but symptoms typically develop in adulthood. The incidence of ARVC is approximately 1 in 1,000 to 1 in 2,500. LVNC is characterized by left ventricular hypertrophy and prominent trabeculations of the ventricular wall, giving a spongy appearance to the muscle wall. It is thought to be caused by the arrest of normal myocardial morphogenesis. Clinical presentation is highly variable, ranging from no symptoms to congestive heart failure and life-threatening arrhythmias. An increased risk of thromboembolic events is also present with LVNC. Approximately 67% of LVNC is considered familial. Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy and is associated with abnormally rigid ventricular walls. Systolic function can be normal or near normal, but diastolic dysfunction is present. There are several nongenetic causes of RCM, but this condition can be familial as well, with the TNNI3 gene accounting for the majority of inherited cases. The age at presentation for familial RCM ranges from childhood to adulthood, and there is an increased risk of sudden death associated with this condition. Noonan syndrome is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, and characteristic facial dysmorphology. HCM is present in approximately 20% to 30% of individuals affected with Noonan syndrome. There are a number of disorders with significant phenotypic overlap with Noonan syndrome, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). Noonan syndrome and related disorders (also called the RASopathies) are caused by variants in genes involved in the RAS-MAPK signaling pathway. In some
cases, variants in these genes may cause cardiomyopathy in the absence of other syndromic features. Cardiomyopathy may also be caused by an underlying systemic disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder. In these cases, cardiomyopathy may be the first feature to come to attention clinically. The hereditary forms of cardiomyopathy are most frequently associated with an autosomal dominant form of inheritance, however X-linked and autosomal recessive forms of disease are also present. In some cases, compound heterozygous or homozygous variants may be present in genes typically associated with autosomal dominant inheritance, often leading to a more severe phenotype. Digenic variants (2 different heterozygous variants at separate genetic loci) in autosomal dominant genes have also been reported to occur in patients with severe disease (particularly HCM and ARVC). The inherited cardiomyopathies display both allelic and locus heterogeneity, whereby a single gene may cause different forms of cardiomyopathy (allelic heterogeneity) and variants in different genes can cause the same form of cardiomyopathy (locus heterogeneity). This comprehensive cardiomyopathy panel includes sequence analysis of 55 genes and may be considered for individuals with HCM, DCM, ARVC, or LVNC, whom have had uninformative test results from a more targeted, disease-specific test. This test may also be helpful when the clinical diagnosis is not clear, or when there is more than 1 form of cardiomyopathy in the family history. It is important to note that the number of variants of uncertain significance detected by this panel may be higher than for the disease-specific panels, making clinical correlation more difficult. Genes included in the Comprehensive Cardiomyopathy Multi-Gene Panel Gene Inheritance Disease Association ABCC9 ATP-binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKR1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM BRAF V-RAF murine sarcoma viral oncogene homolog B1 AD Noonan/CFC/Costello syndrome CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tateyama-type distal myopathy, rippling muscle disease CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder CRYAB Crystallin, alpha-B AD, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, Neurogenic Scapuloponeal Syndrome Kaeser Type, LGMD DSC2 Desmocollin AD, AR ARVC, ARVC + skin and hair findings DSG2 Desmoglein AD ARVC, DCM, Carvalaj syndrome DTNA Dystrobrevin, alpha AD LVNC, CHD GLA Galactosidase, alpha X-linked Fabry disease HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome JUP Junction plakoglobin AD, AR ARVC, Naxos disease KRAS Kras V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome LAMA4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated member protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MAP2K1 Mitogen-activated protein kinase 1 AD Noonan/CFC/Costello syndrome MYBP3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH6 Myosin, heavy chain 6, cardiac muscle, alpha HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light cahin 2, regulatory, cardiac, slow AD HCM MYL3 Myosin, light chain 3, alkali, ventricular, skeletal, slow AD, AR HCM MYLK2 Myosin light chain kinase 2 AD HCM MYOZ2 Myozin 2 AD HCM MYPN Myopalladin AD HCM, DCM NEXN Nexilin AD HCM, DCM NRAS Neuroblastoma RAS viral oncogene homolog AD Noonan syndrome PKP2 Plakophilin 2 AD ARVC PLN Phospholamban AD HCM, DCM PRKAG2 Protein kinase, AMP-activated, noncatalytic, gamma2 AD HCM, Wolff-Parkinson-White syndrome PTPN11 Proetin-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/LEOPARD syndrome RAF1 V-RAF-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome RBM20 RNA-binding motif protein 20 AD DCM RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS SCN5A Sodium channel, voltage gated, type V, alpha subunit AD Brugada syndrome, DCM, Heart block, LQTS, SSS, SIDS SGCD Sarcoglycan, delta AD, AR DCM, LGMD SHOC2 Suppressor of clear, C. elegans, homolog of AD Noonan-syndrome like with loose anagen hair SOS1 Son of sevenless, dropophil, homolog 1 AD Noonan syndrome TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TCAP Titin-cap (teletethin) AD, AR HCM, DCM, LGMD TMEM43 Transmembrane protein 43 AD ARVC, EMD TNNTC1 Troponin C, slow AD HCM, DCM TNNI3 Troponin I, cardiac AD, AR DCM, HCM, RCM TNNT2 Troponin T2, cardiac AD HCM, DCM, LVNC TPM1 Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, ARVC, myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive
cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), congenital heart defect (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary cardiomyopathy Establishing a diagnosis of a hereditary cardiomyopathy, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identification of a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Congenital Adrenal Hyperplasia (CAH) Newborn Screening, Blood Spot**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is a group of disorders caused by inherited defects in steroid biosynthesis, in particular, 21-hydroxylase deficiency (approximately 90% of cases), and 11-beta hydroxylase deficiency (approximately 5-8% of cases). The overall incidence of the classic form of 21-hydroxylase deficiency is approximately 1 in 16,000 worldwide. Individuals with CAH may present with life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females as a result of reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (17-OHP) and androgens. Hormone replacement therapy, when initiated early, enables a significant reduction in morbidity and mortality. Therefore, newborn screening for CAH is desirable and has been implemented in all 50 states. Immunoassays are typically used to quantify 17-OHP as a marker for CAH. However, these immunoassays are hampered by cross-reactivity of the antibodies with other steroids, yielding a high rate of false-positive results. Tandem mass spectrometry allows for the
simultaneous specific determination of 17-OHP and other steroids, such as androstenedione, cortisol, 11-deoxycortisol, and 21-deoxycortisol. Application of this technology to the determination of steroids in newborn screening blood spots significantly enhances the correct identification of patients with CAH and reduces the number of false-positive screening results when implemented as a second-tier analysis performed prior to reporting of initial newborn screen results.

**Useful For:** Second-tier testing of newborns with abnormal screening result for congenital adrenal hyperplasia

**Interpretation:** Findings of a 17-hydroxyprogesterone (17-OHP) value >7.0 ng/mL in males or >4.0 ng/mL in females, and a high (17-OHP + androstenedione)/cortisol ratio (controls: < or =2.5) are supportive of the initial abnormal newborn screening result. Findings of an 11-deoxycortisol value >10.0 ng/mL or 21-deoxycortisol >1.6 ng/mL with elevated 17-OHP further support the abnormal newborn screening result and increase the diagnostic specificity. Clinical and laboratory follow-up is strongly recommended.

**Reference Values:**

**17-HYDROXYPROGESTERONE**
- Males: <7.1 ng/mL
- Females: <4.1 ng/mL

**ANDROSTENEDIONE**
- <3.1 ng/mL

**CORTISOL**
- >2.5 ng/mL

**11-DEOXYCORTISOL**
- <10.1 ng/mL

**21-DEOXYCORTISOL**
- <1.7 ng/mL

**(17 OHP + ANDROSTENEDIONE)/CORTISOL RATIO**
- <2.51
  - Note: Abnormal (17 OHP + Androstenedione)/Cortisol Ratio: >2.5 is only applicable when 17-OHP is elevated

**11-DEOXYCORTISOL/CORTISOL RATIO**
- <1.1

**Clinical References:**

**CAH21**

**Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency**

**Clinical Information:** The cause of congenital adrenal hyperplasia (CAH) is an inherited genetic defect that results in decreased formation of 1 of the many enzymes that are involved in the production of cortisol. The enzyme defect results in reduced glucocorticoids and mineralocorticoids, and elevated 17-hydroxyprogesterone (OHPG) and androgens. The resulting hormone imbalances can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. Adult-onset CAH may result in hirsutism or infertility in females. The adrenal glands, ovaries,
testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 positions to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and the feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequently, increased pituitary release of ACTH increases production of OHPG. In contrast, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-ol-dehydrogenase (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone, respectively. Most (90%) cases of CAH are due to mutations in the 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione with decreased cortisol. By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (DCRN / 11-Deoxycorticosterone, Serum), respectively, are necessary for diagnosis. OHPG is bound to both transcortin and albumin, and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests than pregnanetriol measurement are available to diagnose disorders of steroid metabolism. The CAH profile allows the simultaneous determination of OHPG, androstenedione, and cortisol. These steroids can also be ordered individually (OHPG / 17-Hydroxyprogesterone, Serum; ANST / Androstenedione, Serum; CINP / Cortisol, Serum, LC-MS/MS).

Useful For: Preferred screening test for congenital adrenal hyperplasia (CAH) that is caused by 21-hydroxylase deficiency Part of a battery of tests to evaluate females with hirsutism or infertility, which can result from adult-onset CAH

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-Hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common is 3 beta-hydroxysteroid dehydrogenase type 2 (3 beta HSD-2) deficiency, characterized by low cortisol and substantial elevations in dehydroepiandrosterone sulfate (DHEA-S) and 17-alpha-hydroxypregnenolone, while androstenedione is either low, normal, or rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare steroidogenic acute regulatory protein deficiency, all steroid hormone levels are low and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. OHPG is measured to guide treatment, but this test correlates only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable.

Reference Values:

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<tr>
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<tr>
<td>Stage II</td>
<td>9.8-14.5</td>
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<td>Stage III</td>
<td>10.7-15.4</td>
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<td>Stage IV</td>
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<td>Stage V</td>
<td>12.8-17.3</td>
<td>65-210 Females*</td>
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<th>Tanner Stages</th>
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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
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<td>III</td>
<td>10.0-14.4</td>
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<td>77-225</td>
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<td>V</td>
<td>11.8-18.6</td>
<td>80-240</td>
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17-HYDROXYPROGESTERONE

Children Preterm infants: Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL. Term infants 0-28 days: Levels fall from newborn (to prepubertal gradually within 6 months. Prepubertal males: Prepubertal females: Adults Males: Females Follicular: Luteal: Postmenopausal:


**Clinical References:**

**Congo Red Stain**

**Clinical Information:** Congo red may selectively bind to amyloid. Abnormal deposition of amyloid in various organs may cause dysfunction of the organs. Congo red stain is helpful in the identification of abnormal amyloid deposition in clinical specimens.

**Useful For:** Demonstration of amyloid deposits in tissues, body fluids, or subcutaneous fat aspirations. Aids in the diagnosis of all forms of amyloidosis.

**Interpretation:** Positive staining is indicated by apple-green birefringence utilizing a polarized microscope. The laboratory will provide an interpretive report.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Congo Red Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.
**Connective Tissue Diseases Cascade, Serum**

**Clinical Information:** The following diseases are often referred to as connective tissue diseases: rheumatoid arthritis (RA), lupus erythematosus (LE), scleroderma (systemic sclerosis) CREST syndrome (calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia), Sjogren syndrome, mixed connective tissue disease (MCTD), and polymyositis. Connective tissue diseases (systemic rheumatic diseases) are characterized by immune-mediated inflammation that involves the joints, skin, and visceral organs. These diseases are also accompanied by antibodies to a host of nuclear and cytoplasmic autoantigens. The diagnosis of a connective tissue disease is based on clinical signs and symptoms and characteristic radiographic, histopathologic, and serologic findings. Certain connective tissue diseases are characterized by autoantibodies that are highly specific for individual diseases (see table). Connective tissue diseases often present clinically with signs and symptoms that are nonspecific, including constitutional signs (eg, fever, weight loss, fatigue, and arthralgias). Accordingly, consideration of the possibility of a connective tissue disease is common on initial clinical presentation and testing for antibodies to autoantigens associated with connective tissue diseases is often performed early in the evaluation of many patients.(1) Autoantibodies with High Specificity for Individual Connective Tissue Diseases Cyclic citrullinated peptide antibodies RA dsDNA antibodies LE Scl 70 antibodies (topoisomerase 1) Scleroderma Jo 1 antibodies (histidyl tRNA synthetase) Polymyositis SSA/Ro and SSB/La antibodies Sjogren syndrome RNP antibodies (in isolation) MCTD Sm antibodies LE Ribosome P antibodies LE Centromere antibodies CREST syndrome In CTDC / Connective Tissue Diseases Cascade, serum is tested initially for the presence of antinuclear antibodies (ANA) and for cyclic citrullinated peptide (CCP) antibodies. The presence of CCP antibodies indicates a strong likelihood of RA.(2) The presence of ANA supports the possibility of a connective tissue disease, and the level of ANA is used to identify sera for second-order testing for antibodies to double-stranded DNA (dsDNA) and the other autoantigens. The decision threshold for performing the second-order tests is based on empirical data derived from testing patients with varying levels of ANA and was chosen to minimize testing when positive results for dsDNA and other antibodies are very unlikely.(3)

**Useful For:** This test is designed to evaluate patients with signs and symptoms compatible with connective tissue diseases. The testing algorithm is useful in the initial evaluation of patients and performs best in clinical situations in which the prevalence of disease is low.(4)

**Interpretation:** Interpretive comments are provided. See individual unit codes for additional information.

**Reference Values:**

**ANTINUCLEAR ANTIBODIES (ANA)**

- \(< 1.0\) U (negative)
- \(1.1-2.9\) U (weakly positive)
- \(3.0-5.9\) U (positive)
- \(> 6.0\) U (strongly positive)

Reference values apply to all ages.

**CYCLIC CITRULLINATED PEPTIDE ANTIBODIES, IgG**

- \(< 20.0\) U (negative)
- \(20.0-39.9\) U (weak positive)
- \(40.0-59.9\) U (positive)
- \(> 60.0\) U (strong positive)

Reference values apply to all ages.

Copper, 24 Hour, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an ATP-dependent transporter protein. Mutations in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin, or due to allelic variances in cellular metal ion transporters. Hypercupriuria is also found in Menkes disease (kinky hair disease), hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Low urine copper levels are seen in malnutrition, hypoproteinemias, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

Useful For: Investigation of Wilson disease and obstructive liver disease

Interpretation: Humans normally excrete <60 mcg/day of copper in the urine. Urinary copper excretion >60 mcg/day may be seen in: -Wilson disease -Menkes disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega-dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

Reference Values:
0-15 years: not established
> or =16 years: 15-60 mcg/specimen


Copper, Liver Tissue

Clinical Information: Homeostatic regulation of copper metabolism is very complex. The liver is the key organ to facilitate copper storage and incorporation of copper into the transport protein ceruloplasmin. Intestinal absorption and biliary excretion also play major roles in the regulation of copper homeostasis. Abnormal copper metabolism is associated with liver disease. Elevated serum copper concentrations are seen in portal cirrhosis, biliary tract disease, and hepatitis, probably because excess copper that would normally be excreted in the bile is retained in circulation. In primary biliary cirrhosis, ceruloplasmin is high, resulting in high serum copper. Lesser elevations of hepatic copper are found in chronic copper poisoning, obstructive jaundice, and certain cases of hepatic cirrhosis. Reduced serum copper concentration is typical of Wilson disease (hepatolenticular degeneration). Wilson disease is characterized by liver disease, neurologic abnormalities, and psychiatric disturbances. Kayser-Fleischer rings are normally present and urinary copper excretion is increased, while serum copper and ceruloplasmin are low.

Useful For: Diagnosing Wilson disease and primary biliary cirrhosis

Interpretation: The constellation of symptoms associated with Wilson disease (WD), which includes Kayser-Fleischer rings, behavior changes, and liver disease, is commonly associated with liver copper concentration >250 mcg/g dry weight. >1,000 mcg/g dry weight: VERY HIGH. This finding is virtually diagnostic of WD; such patients should be showing all the signs and symptoms of WD. 250 mcg/g dry
weight to 1,000 mcg/g dry weight: HIGH. This finding is suggestive of WD unless signs and symptoms, supporting histology, and other biochemical results (low serum ceruloplasmin, low serum copper, and high urine copper) are not evident. 35 mcg/g dry weight to 250 mcg/g dry weight: HIGH. Excessive copper at this level can be associated with cholestatic liver disease, such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and familial cholestatic syndrome. The heterozygous carriers for WD occasionally have modestly elevated values, but rarely higher than 125 mcg/g of dry weight. In general, the liver copper content is higher than 250 mcg/g dried tissue in WD patients. In patients with elevated levels of copper without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for WD (WDMS / Wilson Disease Mutation Screen, ATP7B DNA Sequencing) is available at Mayo Clinic.

Reference Values:
10-35 mcg/g dry weight

>1,000 mcg/g dry weight: VERY HIGH
This finding is strongly suggestive of Wilson disease. If this finding is without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for Wilson disease (WDMS / Wilson Disease Mutation Screen, ATP7B DNA Sequencing) is also available at Mayo Clinic. Please call Mayo Medical Laboratories at 800-533-1710 or 507-266-5700 if you need further assistance.

250-1,000 mcg/g dry weight: HIGH
This finding is suggestive of possible Wilson disease. If this finding is without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for Wilson disease (WDMS / Wilson Disease Mutation Screen, ATP7B DNA Sequencing) is also available at Mayo Clinic. Please call Mayo Medical Laboratories at 800-533-1710 or 507-266-5700 if you need further assistance.

35-250 mcg/g dry weight: HIGH
Excessive copper at this level can be associated with cholestatic liver disease, such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and familial cholestatic syndrome. Heterozygous carriers for Wilson disease occasionally have modestly elevated values, but rarely higher than 125 mcg/g of dry weight. In general, the liver copper content is higher than 250 mcg/g dried tissue in patients with Wilson disease. If this finding is without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for Wilson disease (WDMS / Wilson Disease Mutation Screen, ATP7B DNA Sequencing) is also available at Mayo Clinic. Please call Mayo Medical Laboratories at 800-533-1710 or 507-266-5700 if you need further assistance.

Clinical References:

Copper, Random, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an ATP-dependent transporter protein. Mutations in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin, or due to allelic variances in cellular metal ion transporters. Hypercupriuria is also found in Menkes disease (kinky hair disease), hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant
diseases (including leukemia). Urine copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Low urine copper levels are seen in malnutrition, hypoproteinemias, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

**Useful For:** Investigation of Wilson disease and obstructive liver disease

**Interpretation:** Humans normally excrete <60 mcg/L of copper in the urine. Urinary copper excretion >60 mcg/L may be seen in: -Wilson disease -Menkes disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega-dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15 years</td>
<td>not established</td>
</tr>
<tr>
<td>&gt; or =16 years</td>
<td>15-60 mcg/L</td>
</tr>
</tbody>
</table>

**Clinical References:**

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**Copper, Serum**

**Clinical Information:** In serum from normal, healthy humans, more than 95% of the copper is incorporated into ceruloplasmin; the remaining copper is loosely bound to albumin. Low serum copper, most often due to excess iron or zinc ingestion and infrequently due to dietary copper deficit, results in severe derangement in growth and impaired erythropoiesis. Low serum copper is also observed in hepatolenticular degeneration (Wilson disease) due to a decrease in the synthesis of ceruloplasmin and allelic variances in cellular metal ion transporters. In Wilson disease, the albumin-bound copper may actually be increased, but ceruloplasmin copper is low, resulting in low serum copper. However, during the acute phase of Wilson disease (fulminant hepatic failure), ceruloplasmin and copper may be normal; in this circumstance, hepatic inflammation causes increased release of ceruloplasmin. It is useful to relate the degree of liver inflammation to the ceruloplasmin and copper—see discussion on hypercupremia below. Significant hepatic inflammation with normal ceruloplasmin and copper suggest acute Wilson disease. Other disorders associated with decreased serum copper concentrations include malnutrition, hypoproteinemias, malabsorption, nephrotic syndrome, Menkes disease, copper toxicity, and megadosing of zinc-containing vitamins (zinc interferes with normal copper absorption from the gastrointestinal tract). Hypercupremia is found in primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, malignant diseases (including leukemia), thyrotoxicosis, and various infections. Serum copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Since the gastrointestinal (GI) tract effectively excludes excess copper, it is the GI tract that is most affected by copper ingestion. Increased serum concentration does not, by itself, indicate copper toxicity.

**Useful For:** Diagnosis of: -Wilson disease -Primary biliary cirrhosis -Primary sclerosing cholangitis

**Interpretation:** Serum copper below the normal range is associated with Wilson disease, as well as a variety of other clinical situations (see Clinical Information). Excess use of denture cream containing zinc can cause hypocupremia. Serum concentrations above the normal range are seen in primary biliary cirrhosis and primary sclerosing cholangitis, as well as a variety of other clinical situations (see Clinical Information).

**Reference Values:**

- 0-2 months: 0.40-1.40 mcg/mL
- 3-6 months: 0.40-1.60 mcg/mL
- 7-9 months: 0.40-1.70 mcg/mL
10-12 months: 0.80-1.70 mcg/mL
13 months-10 years: 0.80-1.80 mcg/mL
> or =11 years: 0.75-1.45 mcg/mL


Copper/Creatinine Ratio, Random, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an ATP-dependent transporter protein. Mutations in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin, or due to allelic variances in cellular metal ion transporters. Hypercupriuria is also found in Menkes disease (kinky hair disease), hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Low urine copper levels are seen in malnutrition, hypoproteinemias, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

Useful For: Investigation of Wilson disease and obstructive liver disease

Interpretation: Humans normally excrete <60 mcg/g creatinine in the urine. Urinary copper excretion >60 mcg/g creatinine may be seen in: -Wilson disease -Menkes disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega-dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

Reference Values: > or =16 years: 15-60 mcg/g Creatinine
Reference values have not been established for patients that are <16 years of age.


Coriander, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**FCORG**

**Corn IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FCOR4**

**Corn IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**

<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility...
of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**Corn Pollen, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>0.35-0.69</td>
</tr>
<tr>
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<td></td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or = 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**Corn-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Corticosterone Quantitative by HPLC-MS/MS, Serum**

**Reference Values:**

<table>
<thead>
<tr>
<th>Gestation Time, Age</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 28 weeks)</td>
<td>1108 ng/dL</td>
</tr>
<tr>
<td>Premature (29 â€“ 30 weeks)</td>
<td>Not established</td>
</tr>
<tr>
<td>Premature (31 â€“ 35 weeks)</td>
<td>1700 ng/dL</td>
</tr>
<tr>
<td>Full Term Newborn, 1 â€“ 7 days</td>
<td>850 ng</td>
</tr>
<tr>
<td>8 â€“ 29 days</td>
<td>Not Established</td>
</tr>
<tr>
<td>30 days â€“ 11 months</td>
<td>1500 ng/dL</td>
</tr>
<tr>
<td>Age, Draw Time</td>
<td>Reference Interval</td>
</tr>
<tr>
<td>1 â€“ 16 years, morning</td>
<td>1860 ng/dL</td>
</tr>
<tr>
<td>1 â€“ 16 years, evening</td>
<td>620 ng/dL</td>
</tr>
<tr>
<td>17 years and older, morning</td>
<td>820 ng/dL</td>
</tr>
<tr>
<td>17 years and older, evening</td>
<td>Not Established</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT  
800-533-1710 or 507-266-5700 or MayoMedical Laboratories.com
Corticoesterone, Serum

Clinical Information: Corticoesterone is a steroid hormone and a precursor molecule for aldosterone. It is produced from deoxycorticoesterone, further converted to 18-hydroxy corticoesterone and, finally, to aldosterone in the mineralocorticoid pathway. The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions).

Corticoesterone is the first intermediate in the corticoid pathway with significant mineral corticoid activity. Its synthesis from 11-deoxycorticoesterone is catalyzed by 11 beta-hydroxylase 2 (CYP11B2) or by 11 beta-hydroxylase 1 (CYP11B1). Corticoesterone is in turn converted to 18-hydroxycoesterone and finally to aldosterone, the most active mineral corticoid. Both of these reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase (also known as aldosterone synthase) activity. The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17 alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases) and those with the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticoesterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, hirsutism, polycystic ovarian syndrome or infertility, as well as in possible premature adrenarche and pubarche in both genders.

Measurement of the various precursors of mature mineral corticoid and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of corticoesterone is used as an adjunct to 11-deoxycorticoesterone and 11-deoxycortisool (also known as compound S) measurement in the diagnosis of: -CYP11B1 deficiency (associated with cortisol deficiency) -The less common CYP11B2 deficiency (no cortisol deficiency) -The rare glucocorticoid responsive hyperaldosteronism (where expression of the gene CYP11B2 is driven by the CYP11B1 promoter, thus making it responsive to adrenocorticotropic hormone [ACTH] rather than renin) -Isolated loss of function of the 18-hydroxylase or 18-methyloxidase activity of CYP11B2 For other forms of CAH, the following tests might be relevant: -21-Hydroxylase deficiency: - OHPG / 17-Hydroxyprogesterone, Serum - ANST / Androstenedione, Serum - 21DOC / 21-Deoxycortisol, Serum -3-Beta-steroid dehydrogenase deficiency: - 17PRN / Pregnenolone and 17-Hydroxypregnenolone -17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): - 17PRN / Pregnenolone and 17-Hydroxypregnenolone - PGSN / Progesterone, Serum - OHPG / 17-Hydroxyprogesterone, Serum - DHEA / Dehydroepiandrosterone (DHEA), Serum - ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. When evaluating for suspected 11-hydroxylase deficiency, this test should be used in conjunction with measurements of 11-deoxycortisol, 11-corticosteone, 18-hydroxycoesterone, cortisol, renin, and aldosterone. When evaluating congenital adrenal hyperplasia newborn screen-positive children, this test should be used in conjunction with 11-deoxycortisol and 11-deoxycorticosterone measurements as an adjunct to
17-hydroxyprogesterone, aldosterone and cortisol measurements.

**Useful For:** Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11 beta-hydroxylase 1 (CYP11B1) versus 11 beta-hydroxylase 2 (CYP11B2) deficiency, and the diagnosis of glucocorticoid-responsive hyperaldosteronism. Evaluating congenital adrenal hyperplasia newborn screen-positive children, when elevations of 17-hydroxyprogesterone are only moderate, thereby suggesting possible 11-hydroxylase deficiency.

**Interpretation:** In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 microgram/dL for a morning draw). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20 to 300 times) the upper limit of the normal reference range on a morning blood draw. Elevations in 11-deoxycortisol are usually relatively greater than those of 11-deoxycorticosterone because of the presence of intact 11 beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineral corticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineral corticoid results in infants younger than 7 days; mineral corticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require adrenocorticotropic hormone (ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycorticosterol concentration 60 minutes after intravenous or intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2 gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycorticosterol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycorticosterol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycorticosterol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from showing directly responsiveness of mineral corticoid production to ACTH1-24 injection. Normally, this has little, if any, effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineral corticoid levels fall after administration of dexamethasone. Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced, in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of >630 ng/dL (upper limit of reference range for newborns) to 2,000 or 3,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYB11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in these cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires 11-hydroxylation of 17-hydroxyprogesterone.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 552
< or =18 years: 18-1,970 ng/dL
>18 years: 53-1,560 ng/dL


Cortisol, Free and Total

Reference Values:
Adult Reference Ranges for Cortisol, Total:
Males and Females: 8 å€“ 10 AM 4.6 å€“ 20.6 mcg/dL
4 å€“ 6 PM 1.8 å€“ 13.6 mcg/dL

Cortisol Response to ACTH:
Adult Males and Females
Peak >20.0 mcg/dL
Peak >16.0 mcg/dL after IM injection

Adult Reference Ranges for Cortisol, Free:
8:00 å€“ 10:00 AM 0.07 å€“ 0.93 mcg/dL
4:00 å€“ 6:00 PM 0.04 å€“ 0.45 mcg/dL
10:00 å€“ 11:00 PM 0.04 å€“ 0.35 mcg/dL

Cortisol, Free, 24 Hour, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body’s response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) in the urine correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results.

Useful For: Preferred screening test for Cushing syndrome Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency
Interpretation: Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. However, many normal individuals may also exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol measurements cannot be relied upon for the diagnosis of hypocorticalism.

Reference Values:
0-2 years: not established
3-8 years: 1.4-20 mcg/24 hours
9-12 years: 2.6-37 mcg/24 hours
13-17 years: 4.0-56 mcg/24 hours
> or =18 years: 3.5-45 mcg/24 hours

Use the factor below to convert from mcg/24 hours to nmol/24 hours:

Conversion factor
Cortisol: mcg/24 hours x 2.76 = nmol/24 hours (molecular weight=362.5)


**FCORT**
91644

Cortisol, Free, LC/MS/MS

Reference Values:
Adult Reference Ranges for Cortisol, Free, LC/MS/MS:

<table>
<thead>
<tr>
<th>Time</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 - 10:00 AM</td>
<td>0.07 - 0.93 mcg/dL</td>
</tr>
<tr>
<td>4:00 - 6:00 PM</td>
<td>0.04 - 0.45 mcg/dL</td>
</tr>
<tr>
<td>10:00 - 11:00 PM</td>
<td>0.04 - 0.35 mcg/dL</td>
</tr>
</tbody>
</table>

**CRANU**
82920

Cortisol, Free, Random, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic...
corticosteroids, which can affect immunoassay-based cortisol results.

**Useful For:** Investigating suspected hypercortisolism when a 24-hour collection is prohibitive (ie, pediatric patients)

**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. The optimal specimen type for evaluation of primary adrenal insufficiency and hypopituitarism is serum (CORT / Cortisol, Serum).

**Reference Values:**

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 years:</td>
<td>0-2 years:</td>
</tr>
<tr>
<td>3.0-120 mcg/g</td>
<td>3.0-120 mcg/g</td>
</tr>
<tr>
<td>creatinine</td>
<td>creatinine</td>
</tr>
<tr>
<td>3-8 years:</td>
<td>3-8 years:</td>
</tr>
<tr>
<td>2.2-89 mcg/g</td>
<td>2.2-89 mcg/g</td>
</tr>
<tr>
<td>creatinine</td>
<td>creatinine</td>
</tr>
<tr>
<td>9-12 years:</td>
<td>9-12 years:</td>
</tr>
<tr>
<td>1.4-56 mcg/g</td>
<td>1.4-56 mcg/g</td>
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<tr>
<td>creatinine</td>
<td>creatinine</td>
</tr>
<tr>
<td>13-17 years:</td>
<td>13-17 years:</td>
</tr>
<tr>
<td>1.0-42 mcg/g</td>
<td>1.0-42 mcg/g</td>
</tr>
<tr>
<td>creatinine</td>
<td>creatinine</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>&gt; or =18 years:</td>
</tr>
<tr>
<td>1.0-119 mcg/g</td>
<td>0.7-85 mcg/g</td>
</tr>
<tr>
<td>creatinine</td>
<td>creatinine</td>
</tr>
</tbody>
</table>

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine.

<table>
<thead>
<tr>
<th>Conversion factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol mcg/g creatinine x 413=nmol/mol creatinine</td>
</tr>
</tbody>
</table>

| Cortisol molecular weight=362.5 |
| Creatinine molecular weight=149.59 |


**CIVC 6347**

**Cortisol, Inferior Vena Cava, Serum**

**Reference Values:**

No established reference values

**CLAV 6346**

**Cortisol, Left Adrenal Vein, Serum**

**Reference Values:**

No established reference values
Cortisol, Right Adrenal Vein, Serum

Reference Values:
No established reference values

Cortisol, Saliva

Clinical Information: Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). Cushing syndrome results from overproduction of glucocorticoids as a result of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (elevated in the morning) and nadirs (low in the evening) for plasma ACTH and cortisol levels. The diurnal variation is lost in patients with Cushing and these patients have elevated levels of evening plasma cortisol. The measurement of late-night salivary cortisol is an effective and convenient screening test for Cushing syndrome.(1) In a recent study from the National Institute of Health, nighttime salivary cortisol measurement was superior to plasma and urine free cortisol assessments in detecting patients with mild Cushing syndrome.(2) The sensitivity of nighttime salivary cortisol measurements remained superior to all other measures. The distinction between Cushing syndrome and pseudo-Cushing states is most difficult in the setting of mild to moderate hypercortisolism. Subtle increases in salivary cortisol at the midnight cortisol (cortisol of nadir) appear to be 1 of the earliest abnormalities in Cushing syndrome.

Useful For: Screening for Cushing syndrome Diagnosis of Cushing syndrome in patients presenting with symptoms or signs suggestive of the disease

Interpretation: Cushing syndrome is characterized by increased salivary cortisol levels, and late-night saliva cortisol measurements may be the optimum test for the diagnosis of Cushing. It is standard practice to confirm elevated results at least once. This can be done by repeat late-night salivary cortisol measurements, midnight blood sampling for cortisol (CORT / Cortisol, Serum), 24-hour urinary free cortisol collection (CORTU / Cortisol, Free, 24 Hour, Urine), or overnight dexamethasone suppression testing. Upon confirmation of the diagnosis, the cause of hypercortisolism, adrenal versus pituitary versus ectopic adrenocorticotropic hormone production, needs to be established. This is typically a complex undertaking, requiring dynamic testing of the pituitary adrenal axis and imaging procedures. Referral to specialized centers or in-depth consultation with experts is strongly recommended.

Reference Values:
7 a.m.-9 a.m.: 100-750 ng/dL
3 p.m.-5 p.m.: <401 ng/dL
11 p.m.-midnight: <100 ng/dL


Cortisol, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-90% of the plasma corticoids) plays a central role in glucose metabolism and in the body's response to stress. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6 a.m.-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to cortisol-binding globulin (CBG-transcortin) and albumin. Normally, <5% of circulating cortisol is free (unbound). The "free" cortisol is the physiologically active form. Free cortisol is filterable by the renal glomerulus. Although hypercortisolism is uncommon, the
signs and symptoms are common (e.g., obesity, high blood pressure, increased blood glucose concentration). The most common cause of increased plasma cortisol levels in women is a high circulating concentration of estrogen (e.g., estrogen therapy, pregnancy) resulting in increased concentration of cortisol-binding globulin. Spontaneous Cushing syndrome results from overproduction of glucocorticoids as a result of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through the fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Causes of hypocortisolism are: -Addison disease-primary adrenal insufficiency -Secondary adrenal insufficiency: --Pituitary insufficiency --Hypothalamic insufficiency -Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

Useful For: Discrimination between primary and secondary adrenal insufficiency Differential diagnosis of Cushing syndrome

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency, both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. First, the basal plasma ACTH concentration should be measured, followed by the short cosyntropin stimulation test. Other frequently used tests are the metyrapone, and insulin-induced hypoglycemia test. Consult the Endocrine Testing Center at 800-533-1710 extension 4-2148 for testing information and interpretation of test results. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes high-performance liquid chromatography/triple quadrupole-mass spectrometry (LC-MS/MS). A normal result makes the diagnosis unlikely. When cortisol measurement by immunoassay gives results that are not consistent with clinical symptoms, or if patients are known to or suspected of taking exogenous synthetic steroids, consider testing by LC-MS/MS; see CINP / Cortisol, Serum, LC-MS/MS. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum.

Reference Values:
a.m.: 7-25 mcg/dL
p.m.: 2-14 mcg/dL


Cortisol, Serum, LC-MS/MS

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, <5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form, and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal
disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency See Steroid Pathways in Special Instructions.

**Useful For:** Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum. An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome

**Interpretation:** In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

**Reference Values:**
5-25 mcg/dL (a.m.)
2-14 mcg/dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.


well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

**Useful For:** Screening test for Cushing syndrome (hypercortisolism) Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency.

**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (call 800-533-1710). Suppressed cortisol and cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Further, many normal individuals also may exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol measurements cannot be relied upon for the diagnosis of hypocorticalism. Patients with 11-beta HSD deficiency may have cortisone to cortisol ratios <1, whereas a ratio of 2:1 to 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to <1.

**Reference Values:**

**CORTISOL**
- 0-2 years: not established
- 3-8 years: 1.4-20 mcg/24 hours
- 9-12 years: 2.6-37 mcg/24 hours
- 13-17 years: 4.0-56 mcg/24 hours
- > or = 18 years: 3.5-45 mcg/24 hours

**CORTISONE**
- 0-2 years: not established
- 3-8 years: 5.5-41 mcg/24 hours
- 9-12 years: 9.9-73 mcg/24 hours
- 13-17 years: 15-108 mcg/24 hours
- > or = 18 years: 17-129 mcg/24 hours

Use the factors below to convert each analyte from mcg/24 hours to nmol/24 hours:

Conversion factors
- Cortisol: mcg/24 hours x 2.76 = nmol/24 hours (molecular weight=362.5)
- Cortisone: mcg/24 hours x 2.78 = nmol/24 hours (molecular weight=360)

**Clinical References:**
Cortisol/Cortisone, Free, Random, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. It plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

Useful For: Investigating suspected Cushing syndrome ( hypercortisolism), when a 24-hour collection is prohibitive (ie, pediatric patients). Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption

Interpretation: Most patients with Cushing syndrome have increased urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol and cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Patients with 11-beta HSD deficiency may have cortisone to cortisol ratios less than 1, whereas a ratio of 2 or 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to less than 1.

Reference Values:
CORTISOL
Males
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 1.0-119 mcg/g creatinine
Females
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 0.7-85 mcg/g creatinine

**CORTISONE**
0-2 years: 25-477 mcg/g creatinine
3-8 years: 11-211 mcg/g creatinine
9-12 years: 5.8-109 mcg/g creatinine
13-17 years: 5.4-102 mcg/g creatinine
18-29 years: 5.7-153 mcg/g creatinine
30-39 years: 6.6-176 mcg/g creatinine
40-49 years: 7.6-203 mcg/g creatinine
50-59 years: 8.8-234 mcg/g creatinine
60-69 years: 10-270 mcg/g creatinine
> or =70 years: 12-311 mcg/g creatinine

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine:

<table>
<thead>
<tr>
<th>Conversion factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol: mcg/g creatinine x 413=nmol/mol creatinine</td>
</tr>
<tr>
<td>Cortisone: mcg/g creatinine x 415=nmol/mol creatinine</td>
</tr>
</tbody>
</table>

Cortisol molecular weight=362.5
Cortisone molecular weight=360.4
Creatinine molecular weight=149.59

**Clinical References:**

---

**Corynebacterium diphtheriae Culture**

**Clinical Information:** Corynebacterium diphtheriae is the etiological agent of diphtheria and occurs in 2 forms, respiratory and cutaneous diphtheria. Respiratory diphtheria may be further classified into pharyngeal, tonsillar, laryngeal, and the less common anterior nasal diphtheria. Due to vaccination programs in the United States, diphtheria is now a rarely reported disease. Corynebacterium diphtheriae is primarily spread by droplets from coughing or sneezing. The incubation period averages 2 to 5 days. The illness is characterized by fever, malaise, and sore throat with a distinguishing thick pseudomembrane present over the involved mucosa. A swab from beneath the pseudomembrane is the preferred specimen for culture. The organisms multiplying at the infection site produce a toxin, diphtheria toxin, which may result in systemic complications affecting the heart, nervous system, etc. In patients with a clinical diagnosis of possible diphtheria, appropriate specimens should be collected for culture; patients should be placed in appropriate isolation and consideration given to administration of empiric antitoxin (available in the United States through the Centers for Disease Control and prevention) and antibiotics; respiratory and airway support may be required.

**Useful For:** Confirmation of the clinical diagnosis of diphtheria

**Interpretation:** A positive result supports a diagnosis of diphtheria. The pathogenesis of the associated disease relates to production phase-encoded diphtheria toxin. Since isolates of Corynebacterium diphtheriae may or may not harbor genes to produce the toxin, they should be further tested for diphtheria toxin production. A negative result is evidence against a diagnosis of diphtheria but does not definitively rule out this disease since culture may be negative because of prior antimicrobial therapy or organism present below the limit of detection of the assay.

**Reference Values:**
No growth of Corynebacterium diphtheriae
**Cotton Fiber, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**Cottonseed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Cottonwood, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Cow Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Coxiella burnetii (Q fever), Molecular Detection, PCR

Clinical Information: Coxiella burnetii, the causative agent of Q fever, is a small obligate intracellular bacterium, which is associated with animals. It is acquired through aerosol exposure and generally causes mild respiratory disease. A small number of acute cases advance to a chronic infection, which typically manifests as endocarditis. Left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic studies may be nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using PCR may be a useful tool for diagnosing some cases of Coxiella burnetii infection. Mayo Medical Laboratories has developed a real-time PCR test that rapidly detects Coxiella burnetii DNA in clinical specimens by targeting a sequence of the shikimate dehydrogenase gene (aroE) unique to Coxiella burnetii.

Useful For: Diagnosing Coxiella burnetii infection (eg, Q fever)

Interpretation: A positive test is diagnostic of Coxiella burnetii infection. A negative test indicates the absence of detectable Coxiella burnetii DNA, but does not negate the presence of the organism or recent disease and may occur due to sequence variability underlying primers and probes, or the presence of Coxiella burnetii in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

Mayo Medical Laboratories has developed a real-time PCR test that permits rapid identification of Coxiella burnetii. The assay targets a unique sequence of the shikimate dehydrogenase gene (aroE) present in Coxiella burnetii.

**Useful For:** Diagnosing Coxiella burnetii infection (eg, Q fever)

**Interpretation:** A positive test is diagnostic of Coxiella burnetii disease. A negative result does not negate the presence of the organism or active disease, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Coxiella burnetii in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**Coxiella burnetii (Q Fever), Molecular Detection, PCR, Serum**

**Clinical Information:** Coxiella burnetii, the causative agent of Q fever, is a small obligately intracellular bacterium, which is associated with animals. It is acquired through aerosol exposure and generally causes mild respiratory disease. A small number of acute cases advance to a chronic infection, which typically manifests as endocarditis. Left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic studies may be nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using PCR may be a useful tool for diagnosing some cases of Coxiella burnetii infection. Mayo Medical Laboratories has developed a real-time PCR test that rapidly detects Coxiella burnetii DNA in clinical specimens by targeting a sequence of the shikimate dehydrogenase gene (aroE) unique to Coxiella burnetii.

**Useful For:** Diagnosing Coxiella burnetii infection (ie, Q fever)

**Interpretation:** A positive test is diagnostic of Coxiella burnetii infection. A negative result does not negate the presence of the organism or active disease, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Coxiella burnetii in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

FACX 91340

Coxsackie A Antibodies (CSF)

Reference Values:

REFERENCE RANGE: < 1:1

INTERPRETIVE CRITERIA:

< 1:1 Antibody Not Detected
> or = 1:1 Antibody Detected

Diagnosis of infections of the central nervous system is accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

COXA 80248

Coxsackie A Antibodies, Serum

Reference Values:

REFERENCE RANGE: <1:8

INTERPRETIVE CRITERIA:

<1:8 Antibody Not Detected
> or = 1:8 Antibody Detected

Single titers of > or = 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

FBCX 91341

Coxsackie B (1-6) Antibodies, (CSF)

Reference Values:

Reference Range: < 1:1

Interpretive Criteria:

< 1:1 Antibody Not Detected
> or = 1:1 Antibody Detected

Diagnosis of infections of the central nervous system is accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

COXB 80247

Coxsackie B(1-6) Antibodies (Serum)

Reference Values:
Reference Range: <1:8

INTERPRETIVE CRITERIA:

<1:8 Antibody Not Detected
> or = 1:8 Antibody Detected

Single titers of > or = 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

CPOXZ

CPOX Gene, Full Gene Analysis

Clinical Information: Hereditary coproporphyria (HCP) is an autosomal dominant (AD) acute hepatic porphyria that presents with clinical attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HCP is also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. HCP is caused by AD mutations in the CPOX gene. Mutations may have incomplete penetrance. Homozygous mutations in CPOX have been reported in association with a more severe, phenotypically distinct condition called harderoporphyria that is characterized by neonatal hemolytic anemia with mild residual anemia during childhood and adulthood. Affected patients may also present with skin lesions and fecal harderoporphyin accumulation may be observed. This condition is inherited in an autosomal recessive pattern and all patients identified to date have been heterozygous or homozygous for the K404E mutation. For HCP, acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in distinguishing HCP from other forms of acute porphyria.

Useful For: Confirmation of hereditary coproporphyria (HCP) for patients with clinical features. This test should be ordered only for individuals with symptoms suggestive of HCP. Asymptomatic patients with a family history of HCP should not be tested until a mutation has been identified in an affected family member.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

FCRAB

Crab IgG

Interpretation: mcg/mL of IgG
Lower Limit of Quantitation 2.0
Upper Limit of Quantitation 200

Reference Values:
The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**CRAB 82745**

**Crab, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Reference values apply to all ages.


**CRANB 86307**

**Cranberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are...
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**Crayfish, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
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Reference values apply to all ages.


**Clinical Disorders Panel, Urine**

**Clinical Information:** Disorders of creatine synthesis (deficiency of arginine:glycine amidotransferase [AGAT] and guanidinoacetate methyltransferase [GAMT]) and creatine transporter (SLC6A8) deficiency are collectively described as creatine deficiency syndromes (CDS). AGAT and GAMT deficiencies are inherited in an autosomal recessive manner, while the creatine transporter defect is X-linked. All 3 disorders result in a depletion of cerebral creatine and typically present with global developmental delays, intellectual disability, and severe speech delay. Commonly, patients with CDS develop seizures. Patients with GAMT and the creatine transporter deficiency exhibit behavioral problems and features of autism. Female carriers for the creatine transporter deficiency can have intellectual disability and behavioral problems, and some develop seizures. Diagnosis is possible by measuring guanidinoacetate (GAA), creatine (Cr), and creatinine (Crn) in plasma and urine. The profiles are specific for each clinical entity. Patients with GAMT deficiency typically exhibit normal to low Cr, very elevated GAA, and low Crn. Patients with AGAT deficiency typically exhibit normal to low Cr, low GAA, and normal to low Crn. In comparison, elevated Cr, normal GAA, normal to low Crn, and an elevated Cr:Crn ratio characterize patients with creatine transporter defect. Treatment with oral supplementation of creatine monohydrate is available and effective for the AGAT and GAMT deficiencies. Creatine supplementation has not been shown to improve outcomes in males with the creatine transporter defect. Female carriers of creatine transporter deficiency who have symptoms, however, have been reported to benefit from creatine supplementation.

**Useful For:** Evaluation of patients with a clinical suspicion of inborn errors of creatine metabolism including arginine:glycine amidotransferase deficiency, guanidinoacetate methyltransferase deficiency, and creatine transporter (SLC6A8) defect

**Interpretation:** Reports include concentrations of guanidinoacetate, creatine, and creatinine, and a calculated creatine:creatinine ratio. When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical
information, elements of differential diagnosis, and recommendations for additional biochemical testing.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Creatinine (nmol/mL)</th>
<th>Guanidinoacetate (nmol/mL)</th>
<th>Creatine (nmol/mL)</th>
<th>Creatine/Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =31 days</td>
<td>430-5240</td>
<td>9-210</td>
<td>12-2930</td>
<td>0.02-0.93</td>
</tr>
<tr>
<td>32 days-23 months</td>
<td>313-9040</td>
<td>16-860</td>
<td>18-10490</td>
<td>0.02-2.49</td>
</tr>
<tr>
<td>2-4 years</td>
<td>1140-12820</td>
<td>90-1260</td>
<td>200-9210</td>
<td>0.04-1.75</td>
</tr>
<tr>
<td>5-18 years</td>
<td>1190-25270</td>
<td>40-1190</td>
<td>60-9530</td>
<td>0.01-0.96</td>
</tr>
<tr>
<td>&gt;18 years (male)</td>
<td>3854-23340</td>
<td>30-710</td>
<td>7-470</td>
<td>0.00-0.04 Females</td>
</tr>
</tbody>
</table>

**Clinical References:**


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**CKMB**

**Creatine Kinase (CK) MB Isoenzyme, Serum**

**Clinical Information:** There are 3 isoenzymes of creatine kinase (CK)-BB, -MM, and -MB. The primary source of CKMB is myocardium, although it is also found in skeletal muscle. CKMB levels increase with myocardial damage. Extreme elevations of CKMB can also be associated with skeletal muscle cell turnover as in polymyositis and to a lesser degree in rhabdomyolysis. It can also be elevated in cases of carbon monoxide poisoning, crush injuries, pulmonary embolism, hypothyroidism, and muscular dystrophy. While CKMB has been replaced by troponin assays in the workup of many patients with acute chest pain, CKMB may be useful if the initial troponin determination is abnormal or if a hospitalized patient has a suspected reinfarction.

**Useful For:** Serial quantitation of serum creatine kinase MB (CKMB) levels, often performed at admission and 8-hours, 16-hours, and 24-hours after admission, has traditionally been used as an aid in the diagnosis of myocardial injury May be useful if the initial troponin determination is abnormal or if a hospitalized patient has a suspected reinfarction.

**Interpretation:** Creatine kinase MB (CKMB) levels can be detected within 3 to 8 hours of the onset of chest pain, peak within 12 to 24 hours, and usually return to baseline levels within 24 to 48 hours.

**Reference Values:**

Males: < or =7.7 ng/mL

Females: < or =4.3 ng/mL

Creatine Kinase (CK), Serum

Clinical Information: Creatine Kinase (CK) activity is greatest in striated muscle, heart tissue, and brain. The determination of CK activity is a proven tool in the investigation of skeletal muscle disease (muscular dystrophy) and is also useful in the diagnosis of myocardial infarction (MI) and cerebrovascular accidents. Increased levels of CK also can be found in viral myositis, polymyositis, and hypothyroidism. Following injury to the myocardium, such as occurs in acute MI, CK is released from the damaged myocardial cells. A rise in the CK activity can be found 4 to 8 hours after an infarction. CK activity reaches a maximum after 12 to 24 hours and then falls back to the normal range after 3 to 4 days.

Useful For: The determination of creatine kinase is utilized in the diagnosis and monitoring of myocardial infarction and myopathies such as the progressive Duchenne muscular dystrophy.

Interpretation: Serum creatine kinase (CK) activity is greatly elevated, at some time during the course of the disease, in all types of muscular dystrophy, and especially so in Duchenne type, in which levels up to 50 times the upper limit of normal may be encountered. In progressive muscular dystrophy, enzyme activity in serum is highest in infancy and childhood (7-10 years of age) and may be elevated long before the disease is clinically apparent. Quite high values of CK are noted in viral myositis, polymyositis, and similar muscle diseases. However, in neurogenic Parkinsonism, serum enzyme activity is normal. Very high activity is also encountered in malignant hyperthermia. An early rise in CK is also seen after an acute MI, with values peaking at 12 to 24 hours and falling back to normal in 3 to 4 days. Although total CK activity has been used as a diagnostic test for MI, it has been replaced by the troponin T and I immunoassays, and is no longer the laboratory test choice for diagnosing and monitoring acute infarctions. Serum CK activity may increase in patients with acute cerebrovascular disease or neurosurgical intervention and with cerebral ischemia. Serum CK activity also demonstrates an inverse relationship with thyroid activity. About 60% of hypothyroid subjects show an average elevation of CK activity 5-fold over the upper reference limit; elevation of as high as 50-fold may also be found.

Reference Values:

Males
- 6-11 years: 150-499 U/L
- 12-17 years: 94-499 U/L
- > or =18 years: 52-336 U/L

Females
- 6-7 years: 134-391 U/L
- 8-14 years: 91-391 U/L
- 15-17 years: 53-269 U/L
- > or =18 years: 38-176 U/L

Note: Strenuous exercise or intramuscular injections may cause transient elevation of CK.


Creatine Kinase Isoenzyme Reflex, Serum

Clinical Information: Creatine kinase (CK) activity is found in the cytoplasm of several human tissues; major sources of CK include skeletal muscle, myocardium, and the brain. Cytoplasmic CK isoenzymes are dimers of the subunits M and B (MM, MB, or BB). Brain tissue contains predominantly CK-BB (CK1). Skeletal muscle contains almost exclusively CK-MM (CK3). The myocardium contains approximately 30% of CK-MB (CK2), which has been called the "heart specific" isoenzyme. CK-MB is increased in acute myocardial infarction. Mitochondrial CK, located at the outer surface of the inner mitochondrial membrane, has been suggested to catalyze the rate-limiting step of energy transfer from mitochondrial adenosine triphosphate (ATP) with the formation of creatine phosphatase (CP). The CP molecule, which is smaller in size than ATP, diffuses to target organelles in the cytoplasm where its energy is transferred to ATP by cytoplasmic CK. CK activity results in nonaerobic production of ATP in...
muscle tissues during work. Macro CK refers to at least 2 forms of CK. Macro CK type I is an antibody bound form of cytoplasmic CK. It migrates between CK-MM and CK-MB. Macro CK type II (mitochondrial CK) migrates slightly cathodic of CK-MM. Detection of macro forms of CK is the primary reason for electrophoresis of CK activity.

**Useful For:** Detection of macro forms of creatine kinase Diagnosing skeletal muscle disease, in conjunction with aldolase

**Interpretation:** Creatine kinase (CK)-MB appears in serum 4 to 6 hours after the onset of pain in a myocardial infarction, peaks at 18 to 24 hours, and may persist for 72 hours. CK-MB may also be elevated in cases of carbon monoxide poisoning, pulmonary embolism, hypothyroidism, crush injuries, and muscular dystrophy. Extreme elevations of CK-MB can be associated with skeletal muscle cell turnover as in polymyositis, and to a lesser degree in rhabdomyolysis, as seen in strenuous exercise, particularly in the conditioned athlete. CK-BB can be elevated in patients with head injury, in neonates, and in some cancers such as prostate cancer and small cell carcinoma of the lung. It can also be elevated in other malignancies; however, the clinical usefulness of CK-BB as a tumor marker needs further investigation. The presence of macro CK can explain an elevation of total CK. It does not rise and fall as rapidly as CK-MM and CK-MB in muscle injury. Macro CK type II (mitochondrial CK) is rarely observed. It is only seen in acutely ill patients with malignancies and other severe illnesses with a high associated mortality, such as liver disease and hypoxic injury.

**Reference Values:**

**CREATINE KINASE, TOTAL**

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>6-11 years</td>
<td>150-499 U/L</td>
</tr>
<tr>
<td>12-17 years</td>
<td>94-499 U/L</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>52-336 U/L</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>6-7 years</td>
<td>134-391 U/L</td>
</tr>
<tr>
<td>8-14 years</td>
<td>91-391 U/L</td>
</tr>
<tr>
<td>15-17 years</td>
<td>53-269 U/L</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>38-176 U/L</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are less than 6 years of age.

Note: Strenuous exercise or intramuscular injections may cause transient elevation of CK.

**CREATINE KINASE ISOENZYMES**

<table>
<thead>
<tr>
<th>Isoenzymes</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>100%</td>
</tr>
<tr>
<td>MB</td>
<td>0%</td>
</tr>
<tr>
<td>BB</td>
<td>0%</td>
</tr>
</tbody>
</table>


**Creatinine Clearance, Serum and 24-Hour Urine**

**Clinical Information:** Glomerular filtration rate (GFR) is the sum of filtration rates in all functioning nephrons and so an estimation of the GFR provides a measure of functioning nephrons of the kidney. A decrease in GFR implies either progressive renal disease, or a reversible process causing decreased nephron function (eg, severe dehydration). One of the most common methods used for estimating GFR is creatinine clearance. Creatinine is derived from the metabolism of creatine from skeletal muscle and dietary meat intake, and is released into the circulation at a relatively constant rate. Thus, the serum creatinine concentration is usually stable. Creatinine is freely filtered by glomeruli and not reabsorbed or metabolized by renal tubules. However, approximately 15% of excreted urine creatinine is derived from proximal tubular secretion. Because of the tubular secretion of creatinine, the creatinine clearance typically overestimates the true GFR by 10% to 15%. Creatinine clearance is usually determined from measurement of creatinine in a 24-hour urine specimen and from a serum specimen obtained during the same collection period. The creatinine clearance is then calculated by the equation: 2.54 cm=1 inch 1
kg=2.2 pounds (lbs) Patient surface area (SA)=wt (kg)(.425) X ht (cm)(.725) X 0.007184 Urine conc (mg/dL) x 24 hr Urine volume (mL) Uncorr creat clear= 1440 minutes______ =mL/min Plasma creat (mg/dL) Urine conc (mg/dL) x 24 hr urine volume (mL) Corr creat clear= 1440 minutes______ x 1.73m(2)= mL/min/1.73m(2) Plasma creat (mg/dL) Patient SA

**Useful For:** Estimation of glomerular filtration rate

**Interpretation:** Decreased creatinine clearance indicates decreased glomerular filtration rate (GFR). This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible, including drug effects or decreases in effective renal perfusion (eg, volume depletion, heart failure). Increased creatinine clearance is often referred to as hyperfiltration and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It may also occur with large dietary protein intake. A major limitation of creatinine clearance is that its accuracy worsens in relation to the amount of tubular creatinine secretion. Often as GFR declines, the contribution of urine creatinine from tubular secretion increases, further increasing the discrepancy between true GFR and measured creatinine clearance.

**Reference Values:**

**Creatinine Clearance:**

**Males:**
- 0-18 years: Reference values have not been established
- 19-75 years: 77-160 mL/min/BSA
- > or =76 years: Reference values have not been established

**Females:**
- 0-17 years: Reference values have not been established
- 18-29 years: 78-161 mL/min/BSA
- 30-39 years: 72-154 mL/min/BSA
- 40-49 years: 67-146 mL/min/BSA
- 50-59 years: 62-139 mL/min/BSA
- 60-72 years: 56-131 mL/min/BSA
- > or =73 years: Reference values have not been established

**Creatinine, Urine:** reported in units of mg/dL

**Creatinine, Serum**

**Males**
- 12-24 months: 0.1-0.4 mg/dL
- 3-4 years: 0.1-0.5 mg/dL
- 5-9 years: 0.2-0.6 mg/dL
- 10-11 years: 0.3-0.7 mg/dL
- 12-13 years: 0.4-0.8 mg/dL
- 14-15 years: 0.5-0.9 mg/dL
- > or =16 years: 0.8-1.3 mg/dL

**Females**
- 13-36 months: 0.1-0.4 mg/dL
- 4-5 years: 0.2-0.5 mg/dL
- 6-8 years: 0.3-0.6 mg/dL
- 9-15 years: 0.4-0.7 mg/dL
- > or =16 years: 0.6-1.1 mg/dL

Reference values have not been established for patients that are less than 12 months of age.

Clinical Information: Creatinine: In muscle metabolism, creatinine is synthesized endogenously from creatine and creatine phosphate. Creatinine is removed from plasma by glomerular filtration into the urine without being reabsorbed by the tubules to any significant extent. Renal tubular secretion also contributes a small quantity of creatinine to the urine. As a result, creatinine clearance often overestimates the true glomerular filtration rate (GFR) by 10% to >20%. Determinations of creatinine and renal clearance of creatinine are of value in the assessment of kidney function. Serum or blood creatinine levels in renal disease generally do not increase until renal function is substantially impaired. Estimated GFR (eGFR): Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with chronic kidney disease (CKD) and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Studies have shown that GFR can be reliably estimated from serum creatinine in adults by utilizing the Modification of Diet in Renal Disease (MDRD) Study equation, which includes the patient's age, sex, and race. In Caucasian and African American populations between the ages of 18 and 70 with impaired kidney function (eGFR <60 mL/min/1.73 m[2]), the MDRD equation has been validated at length and is considered the best available means to estimate GFR from creatinine. Estimation of GFR using the MDRD equation has demonstrated good correlation with measured iothalamate clearance in patients with all common causes of kidney disease, including kidney transplant recipients. However, MDRD eGFR significantly underestimates true GFR in patients with normal renal function (eGFR >60 mL/min/1.73 m[2]). Some advantages of the estimated GFR calculation are listed in the following paragraphs: - GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age, sex, and, to a lesser extent, race, on creatinine production further cloud interpretation. - Creatinine is commonly measured in routine clinical practice. Microalbuminuria may be a more sensitive marker of early renal disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. - Monitoring of kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. - The MDRD equation is the most thoroughly validated of the estimating equations. It has been extensively validated in patients with CKD and is currently being evaluated for other populations such as people with normal GFR, people with diabetes, and Hispanics. New equations, or modifications of the MDRD equation, may be necessary in these groups. - The MDRD equation is superior to other methods of estimating GFR. The MDRD equation correlates better with measured GFR than other equations, including the Cockcroft-Gault equation. The MDRD equation is also superior to a 24-hour creatinine clearance measurement. Measured iothalamate clearance remains the gold standard for measuring GFR. - Nephrology specialists already routinely use estimating equations. It has long been appreciated among nephrologists that serum creatinine alone is an insensitive index of GFR. Therefore, renal specialists have employed estimating equations to convert serum creatinine to an approximate GFR. Reporting eGFR values with serum creatinine results allows primary care providers and specialists in other fields to better interpret their results. - The MDRD equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m[2]) using sex, age, and race. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The MDRD equation does require race (African American or non-African American), which also may not be readily available. For this reason, eGFR values for both African Americans and non-African Americans are reported. The difference between the 2 estimates is typically about 20%. The patient or provider can decide which result is appropriate for a given patient.

Useful For: Creatinine: - Diagnosing and monitoring treatment of acute and chronic renal diseases - Adjusting dosage of renally excreted medications - Monitoring renal transplant recipients Estimated Glomerular Filtration Rate (eGFR): Serum creatinine measurement is used in estimating GFR for people with chronic kidney disease (CKD) and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease).

Interpretation: Creatinine: Because serum creatinine is inversely correlated with glomerular filtration rate (GFR), when renal function is near normal, absolute changes in serum creatinine reflect larger changes than do similar absolute changes when renal function is poor. For example, an increase in serum
creatinine from 1 to 2 mg/dL may indicate a decrease in GFR of 50 mL/min (from 100 to 50 mL/min), whereas an increase in serum creatinine level from 4 to 5 mg/dL may indicate a decrease of only 5 mL/min (from 25 to 20 mL/min). Because of the imprecision of serum creatinine as an assessment of GFR, there may be clinical situations where a more accurate GFR assessment must be performed, iothalamate or inulin clearance are superior to serum creatinine. Several factors may influence serum creatinine independent of changes in GFR. For instance, creatinine generation is dependent upon muscle mass. Thus, young, muscular males may have significantly higher serum creatinine levels than elderly females, despite having similar GFRs. Also, because some renal clearance of creatinine is due to tubular secretion, drugs that inhibit this secretory component (eg, cimetidine and trimethoprim) may cause small increases in serum creatinine without an actual decrease in GFR. Estimated GFR: Chronic kidney disease (CKD) is defined as the presence of: persistent and usually progressive reduction in GFR (GFR <60 mL/min/1.73 m²) and/or albuminuria (>30 mg of urinary albumin per gram of urinary creatinine), regardless of GFR. According to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) classification, among patients with CKD, irrespective of diagnosis, the stage of disease should be assigned based on the level of kidney function: Stage Description GFR mL/min/1.73 m² 1 Kidney damage with normal or increased GFR 90 2 Kidney damage with mild decrease in GFR 60 to 89 3 Moderate decrease in GFR 30 to 59 4 Severe decrease in GFR 15 to 29 5 Kidney failure <15 (or dialysis)

**Reference Values:**

**CREATININE**

**Males**
- 1-2 years: 0.1-0.4 mg/dL
- 3-4 years: 0.1-0.5 mg/dL
- 5-9 years: 0.2-0.6 mg/dL
- 10-11 years: 0.3-0.7 mg/dL
- 12-13 years: 0.4-0.8 mg/dL
- 14-15 years: 0.5-0.9 mg/dL
- > or =16 years: 0.8-1.3 mg/dL

Reference values have not been established for patients that are <12 months of age.

**Females**
- 1-3 years: 0.1-0.4 mg/dL
- 4-5 years: 0.2-0.5 mg/dL
- 6-8 years: 0.3-0.6 mg/dL
- 9-15 years: 0.4-0.7 mg/dL
- > or =16 years: 0.6-1.1 mg/dL

Reference values have not been established for patients that are <12 months of age.

**ESTIMATED GFR**
- >60 mL/min/BSA

Note: eGFR results will not be calculated for patients <18 or >70 years old.

**Clinical References:**
Creatinine, 24 Hour, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate.

Useful For: Urinary creatinine, in conjunction with serum creatinine, is used to calculate the creatinine clearance, a measure of renal function.

Interpretation: 24-Hour urinary creatinine determinations are principally used for the calculation of creatinine clearance. Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (e.g. volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
Normal values mg per 24 hours:
Males: 955-2936 mg/24 hours
Females: 601-1689 mg/24 hours

Reference ranges for male and female patients <18 and >83 years of age have not been established.

The expected urine creatinine excretion per 24 hours:
Males: 13-29 mg/kg of body weight/24 hours
Females: 9-26 mg/kg of body weight/24 hours

Reference ranges for male and female patients <18 and >83 years of age have not been established.

Note: To convert to mg/kg of body weight/24 hours, divide the mg/24 h result by body weight in kg.


Creatinine, Body Fluid

Clinical Information: By-products of nitrogen metabolism are elevated in high concentration in urine compared to blood, and serve as a surrogate marker for the identification of urine leakage into a body compartment. This may occur due to trauma, abdominal or pelvic surgery, and bladder perforation. (1,2) Concentrations of creatinine or urea nitrogen that exceed the concentration found in a concurrent sample of blood are suggestive of the presence of urine.(1,3)

Useful For: Identifying the presence of urine as a cause for accumulation of fluid in a body compartment

Interpretation: Body fluid to serum ratios >1.0 suggest the presence of urine in the sample.

Reference Values:
Creatinine, Random, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate (GFR). Since creatinine for the most part in the urine only comes from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

Useful For: Urinary creatinine, in conjunction with serum creatinine, is used to calculate the creatinine clearance, a measure of renal function. In a random specimen, urinary analytes can be normalized by the creatinine concentration to account for the variation in urinary concentrations between subjects.

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
No established reference values


Cri-du-chat, 5p Deletion, FISH

Clinical Information: This test is appropriate for individuals with clinical features suggestive of cri-du-chat syndrome. Cri-du-chat syndrome is associated with a deletion on the short arm of chromosome 5 (5p-). The syndrome can be suspected in infants with a plaintive, mewing cry, low birth weight, and failure to thrive. The weak kitten-like cry that gives name to the syndrome is at least partly due to anatomic abnormalities of the larynx and although the cry changes with time, it does not become normal. Facial features include microcephaly, round face, low-set ears, strabismus, hypertelorism (wide-set eyes), and epicanthus (a vertical fold of skin on either side of the nose). The hands and feet are small, and the hands often have a single crease extending across the palm (simian crease). With age, premature gray hair, dental malocclusion, inguinal hernia, distasis recti, (a separation of the left and right side of the rectus abdominis muscle), and scoliosis are common. Affected individuals' intelligence varies widely from mild-to-severe mental retardation. FISH studies are highly specific and do not exclude other chromosome abnormalities. We recommend that patients suspected of having cri-du-chat syndrome also have conventional chromosome studies (CHRCB / Chromosomes Analysis, Congenital Disorders, Blood)
performed to rule out other chromosome abnormalities or translocations. Additional critical genes associated with cri-du-chat syndrome may lie distal to the loci in this probe set, and this test may give normal results if a microdeletion occurs outside the region tested by this probe. If this test is normal and the patient's phenotype is consistent with cri-du-chat syndrome, subtelomeric FISH analysis may be warranted (TELOF / Subtelomeric Region Anomalies, FISH).

**Useful For:** Establishing a diagnosis of cri-du-chat syndrome Detecting cryptic rearrangements involving 5p15.2 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern (2 signals) in each metaphase is considered negative for a deletion in the region tested by this probe (see Cautions). Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the region tested by this probe.

**Reference Values:**
An interpretive report will be provided.


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**Cryoglobulin and Cryofibrinogen Panel, Serum and Plasma**

**Clinical Information:** Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins are classified as: -Type I (monoclonal) -Type II (mixed--2 or more immunoglobulins of which 1 is monoclonal) -Type III (polyclonal--in which no monoclonal protein is found) Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia. A cryoprecipitate that is seen in plasma but not in serum is caused by cryofibrinogen. Cryofibrinogens are extremely rare and can be associated with vasculitis. Due to the rarity of clinically significant cryofibrinogenemia, testing for cryoglobulins is usually sufficient for investigation of cryoproteins.

**Useful For:** Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
CRYGLOBULIN
Negative (positives reported as percent)
If positive after 1 or 7 days, immunotyping of the cryoprecipitate is performed at an additional charge.

CRYOFIBRINOGEN
Negative
Quantitation and immunotyping will not be performed on positive cryofibrinogen.

**Cryoglobulin, Serum**

**Clinical Information:** Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins are classified as: -Type I (monoclonal) -Type II (mixed--2 or more immunoglobulins of which 1 is monoclonal) -Type III (polyclonal--in which no monoclonal protein is found) Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia.

**Useful For:** Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases
Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Negative (positives reported as percent)


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**Cryptococcus Antigen Screen with Titer, Serum**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. Cryptococcus neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. Cryptococcus gatti was previously only associated with tropical and subtropical regions, however more recently this organism has also been found to be endemic in British Columbia and among the pacific northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of Cryptococcus neoformans infections occur in immunocompromised patient populations, Cryptococcus gattii is has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** An aid in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay screen are automatically repeated with the same method utilizing dilutions in order to generate a titer value. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate
therapy and the resolution of infection.(3)

**Reference Values:**
Negative


**Cryptococcus Antigen Screen with Titer, Spinal Fluid**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. Cryptococcus neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. Cryptococcus gattii was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of Cryptococcus neoformans infections occur in immunocompromised patient populations, Cryptococcus gattii has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis, which test positive by LFA, should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

**Useful For:** Aids in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions in order to generate a titer value. CSF specimens submitted for initial diagnosis, which test positive by LFA, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

**Reference Values:**
Negative

Cryptococcus Antigen Titer, LFA, Serum

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. Cryptococcus neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. Cryptococcus gattii was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of Cryptococcus neoformans infections occur in immunocompromised patient populations, Cryptococcus gattii is has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Monitoring Cryptococcus antigen titers in serum Aiding in the diagnosis of cryptococcosis

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4)

Reference Values:
Negative


Cryptococcus Antigen Titer, LFA, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. Cryptococcus neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. Cryptococcus gattii was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of Cryptococcus neoformans infections occur in immunocompromised patient populations, Cryptococcus gattii is has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Monitoring Cryptococcus antigen titers in cerebrospinal fluid Aiding in the diagnosis of cryptococcosis

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4)

Reference Values:
Negative

nature, particularly weathered pigeon droppings. Cryptococcus gatti was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of Cryptococcus neoformans infections occur in immunocompromised patient populations, Cryptococcus gatti is has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis which test positive by the lateral flow assay should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples which are submitted to monitor Cryptococcus antigen titers during treatment.

**Useful For:** Monitoring Cryptococcus antigen titers in cerebrospinal fluid Aiding in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid; CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4) CSF specimens submitted for initial diagnosis, which test positive by the lateral flow assay, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gatti) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured.

**Reference Values:**
Negative

**Clinical References:**

**LFACX 62703**

**Cryptococcus Antigen with Reflex, LFA, Spinal Fluid**

**Clinical Information:** See individual test IDs

**Useful For:** See individual test IDs

**Interpretation:** See individual test IDs

**Reference Values:**

**CRYPTOCOCCUS ANTIGEN SCREEN WITH TITER**
Negative

**CRYPTOCOCCUS ANTIGEN TITER, LFA**
Fungal Culture
Negative
If positive, fungus will be identified.

Clinical References: See individual test IDs

Cryptococcus Antigen, Pleural Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality in CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of pulmonary cryptococcosis

Interpretation: The presence of cryptococcal antigen in any body fluid is indicative of cryptococcosis. Higher titers appear to correlate with more severe infections. Declining titers in serum may indicate regression of infection or response to therapy. However, monitoring titers to cryptococcal antigen should not be used as a test of cure, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection. In addition to testing for cryptococcal antigen, patients with presumed pulmonary disease due to Cryptococcus neoformans should have respiratory specimens (e.g., bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

Reference Values:
Negative


Cryptococcus Antigen, Urine

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality in CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of cryptococcosis

Interpretation: The presence of cryptococcal antigen in any body fluid is indicative of cryptococcosis. Higher titers appear to correlate with more severe infections. Declining titers in urine or serum may indicate regression of infection or response to therapy. However, monitoring titers to cryptococcal antigen should not be used as a test of cure, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection. In addition to testing for cryptococcal antigen, patients
with presumed disease due to Cryptococcus neoformans should have clinical specimens (eg, bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

**Reference Values:**
Negative


**CRYPS 80335**

**Cryptosporidium Antigen, Feces**

**Clinical Information:** Cryptosporidia are protozoa of the coccidian group which are common parasites of livestock animals and can contaminate and survive in surface water supplies. Infection of humans occurs by the fecal-oral route or by ingestion of contaminated water. The exact mechanism by which the organism causes gastroenteritis is unknown. Cryptosporidiosis occurs as a profuse diarrhea in patients with AIDS and as a self-limited moderate diarrhea in young children, especially daycare attendees and their relatives. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Establishing the diagnosis of intestinal cryptosporidiosis

**Interpretation:** A positive enzyme-linked immunosorbent assay (ELISA) indicates the presence of antigens of cryptosporidium and is interpreted as evidence of infection with that organism. The sensitivity, specificity, and positive predictive value of the ELISA were 87%, 99%, and 98% respectively, as determined by examination of 231 fecal specimens by conventional microscopy and by ELISA.

**Reference Values:**
Negative


**SFC 8719**

**Crystal Identification, Synovial Fluid**

**Clinical Information:** Birefringent crystals are found in the synovial fluid of >90% of patients with acutely inflamed joints. Monosodium urate crystals are seen in gouty fluids and calcium pyrophosphate crystals are seen in chondrocalcinosis. The urates are usually needle-shaped, and the calcium crystals are often rhomboidal. Cholesterol crystals may also be observed.

**Useful For:** Providing a definitive diagnosis for joint disease

**Interpretation:** Positive identification of crystals provides a definitive diagnosis for joint disease.

**Reference Values:**
None seen
If present, crystals are identified.

**Clinical References:** Kjeldsberg C, Knight J: Body fluids: Laboratory examination of cerebrospinal, seminal, serous and synovial fluids. Third edition. Chicago, American Society of Clinical Pathologists, 1993 pp 272-283, 292-293

**CSF3R 64604**

**CSF3R Exon 14 and 17 Mutation Detection by Sanger Sequencing**

**Clinical Information:** CSF3R encodes the receptor for colony-stimulating factor 3, a cytokine that
controls the production, differentiation, and function of granulocytes. Somatic CSF3R mutations were recently described in 50% to 80% of chronic neutrophilic leukemia (CNL) patients. Their association with atypical chronic myelogenous leukemia (aCML) remains controversial. They have also been reported as somatic events in severe congenital neutropenia (SCN) patients. There are 2 types of CSF3R mutations: extracellular domain/membrane proximal point mutations (most commonly p.T618I) and cytoplasmic tail truncation mutations. They demonstrated sensitivity to JAK kinase inhibitors and Src kinase inhibitors, respectively, in vitro assays. In CNL, the most common mutation is p.T618I, although cytoplasmic truncation mutation can also occur. Somatic cytoplasmic truncation mutations have been reported in approximately 30% of SCN patients and 80% of SCN patients with leukemic transformation, who are often on granulocyte-colony stimulating factor (GCSF) therapy. However, their role in leukemic transformation is uncertain.

Useful For: Evaluation and classification of chronic neutrophilia Aids in the diagnosis of chronic neutrophilic leukemia (CNL) Mutation identification may suggest the class of kinase inhibitor to which the neoplasm may be sensitive.

Interpretation: The results will be given as positive or negative for CSF3R mutation and, if positive, the mutation will be described.

Reference Values: An interpretive report will be provided


CTRCZ CTRC Gene, Full Gene Analysis

Clinical Information: Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic, or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. The most common monogenic cause of hereditary pancreatitis, in which a single gene mutation confers major risk susceptibility to chronic pancreatitis, is the presence of a mutation in the PRSS1 gene. However, mutations in CTRC have also been observed in individuals with chronic pancreatitis in association with other risk factors such as mutations in CFTR or SPINK1 or specific environmental risk factors. Thus, in some cases, chronic pancreatitis may be attributable to the presence of CTRC mutations in the context of other risk factors as opposed to CTRC mutations alone. Genetic testing for all 4 pancreatitis susceptibility genes, including CTRC, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

Useful For: Identification of gene mutations contributing to pancreatitis in an individual or family Identification of gene mutations to allow for predictive/diagnostic testing in family members

Interpretation: All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

**CU Index**

**Reference Values:**

< 10.0

The CU Index test is the second generation Functional Anti-FceR test. Patient with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease.

**CU Index Panel**

**Reference Values:**

- Anti-Thyroid Peroxidase IgG: < 35 IU/mL
- Anti-Thyroglobulin IgG: < 40 IU/mL
- TSH (Thyrotropin): 0.4 – 4.0 uIU/mL
- CU Index: < 10.0

The CU Index test is the second generation Functional Anti-FceR test. Patients with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports autoimmune basis for disease.

**Cucumber IgG**

**Interpretation:** mcg/mL of IgG

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Cucumber, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat...
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Cultivated Oat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
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<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.


**CRYE 82918**

**Cultivated Rye, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
</table>

Cultivated Wheat, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Culture Referred for Identification, Fungus

Clinical Information: Organisms are referred for identification or to confirm an identification made elsewhere. This may provide helpful information regarding the significance of the organism, its role in the
disease process, and its possible origin.

**Useful For:** Identification of pure isolates of filamentous fungi and yeast

**Interpretation:** Genus and species are reported on fungal isolates whenever possible.

**Reference Values:**
Not applicable


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**Culture Referred for Identification, Mycobacterium and Nocardia**

**Clinical Information:** There are over 170 recognized species of mycobacteria and more than 100 Nocardia species. Many of these species are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, there are other aerobic actinomycete genera that can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Nucleic acid hybridization probes are utilized that identify specific ribosomal RNA sequences of Mycobacterium tuberculosis complex, Mycobacterium avium complex, and Mycobacterium gordonae. Other Mycobacteria species, Nocardia species and other aerobic actinomycete genera are identified using MALDI-TOF mass spectrometry or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene.

**Useful For:** Rapid identification to the species level for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates

**Interpretation:** Organisms growing in pure culture are identified to the species level whenever possible.

**Reference Values:**
Not applicable

**Clinical References:**

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**Culture Referred for Identification, Virus**

**Clinical Information:** See specific virus

**Useful For:** Viral identification and confirmation

**Interpretation:** See specific virus

**Reference Values:**
Not applicable

**Clinical References:** Depends upon specific virus

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**Cumin Seed (Cuminum cyminum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Curvularia lunata, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; .10</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
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<td>0.70-3.49</td>
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</tr>
<tr>
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<td>3.50-17.4</td>
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<td>High Positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Very High Positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Very High Positive</td>
</tr>
</tbody>
</table>


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**Curvularia spicifera/Bipolaris IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 < .10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.9 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

< 0.35 kU/L

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**Cutaneous Anaplastic Large Cell Lymphoma, 6p25.3 (DUSP22 or IRF4) Rearrangement, FISH, Tissue**

**Clinical Information:** Anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL) is a systemic CD30-positive T-cell lymphoma that was included as a provisional entity in the 2008 World Health Organization (WHO) classification of hematopoietic neoplasms. By definition, ALK-negative ALCL resembles ALK-positive ALCL, but lacks ALK protein or ALK gene rearrangements. It affects predominantly adults with a male to female ratio of about 1.5 to 1. ALK-negative ALCL typically involves lymph nodes and sometimes extranodal sites. ALK-negative
ALCL must be distinguished clinically from primary cutaneous ALCL, which also is usually ALK-negative. Recurrent rearrangements of the DUSP22(IRF4) (dual-specificity phosphatase-22, interferon regulatory factor-4) gene locus on 6p25.3 have been described in CD30-positive T-cell lymphomas and lymphoproliferative disorders, including systemic ALK-negative ALCL, primary cutaneous ALCL, and lymphomatoid papulosis. The presence of this rearrangement has potential prognostic significance in ALCL. Specifically, systemic ALK-negative ALCLs with rearrangements of DUSP22(IRF4), but without rearrangements of TP63 on 3q28 have been reported to be associated with favorable clinical outcomes similar to those in systemic ALK-negative ALCL. The frequency of these rearrangements in ALK-negative ALCL was reported to be 30% in a recent series; therefore, absence of a DUSP22(IRF4) rearrangement does not exclude ALK-negative ALCL. Because a similar frequency of this rearrangement has been reported in primary cutaneous ALCL (28% in 1 recent report), the presence of a DUSP22(IRF4) rearrangement does not distinguish between systemic ALK-negative ALCL and primary cutaneous ALCL, and does not eliminate the need for, or take precedence over, collecting a thorough clinical history and staging. This test does not distinguish between rearrangements localized to the DUSP22 gene and those localized to the IRF4 gene. IRF4 rearrangements are seen in rare CD30-negative T-cell lymphomas, a subset of multiple myelomas, and occasional B-cell lymphomas of various subtypes. Clinical utility for demonstrating their presence in these other neoplasms has not been established. For other FISH testing for T-cell disorders in tissues, see: -TP63F / Peripheral T-Cell Lymphoma (PTCL), TP63 (3q28) Rearrangement, FISH, Tissue -TLYMF / T-Cell Lymphoma, FISH, Tissue

Useful For: Providing potentially prognostic information in patients with documented systemic anaplastic lymphoma kinase-negative anaplastic large cell lymphoma

Interpretation: Systemic anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL) with rearrangements of DUSP22(IRF4) but without rearrangements of TP63 on 3q28 have been associated with favorable clinical outcomes. Therefore, presence or absence of a TP63 rearrangement needs to be determined to interpret this test accurately. The clinical significance of identifying this rearrangement in cutaneous CD30-positive T-cell lymphoproliferative disorders, including primary cutaneous ALCL and lymphomatoid papulosis, has not been established. Furthermore, other T- and B-lineage neoplasms can demonstrate this finding. Clinical and pathologic correlation is recommended. A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the DUSP22(IRF4) probe set. A negative result suggests that an DUSP22(IRF4) gene rearrangement is not present, but does not exclude the diagnosis of ALCL.

Reference Values: An interpretive report will be provided.


Cutaneous Immunofluorescence Antibodies (IgG), Serum

Clinical Information: IgG anti-basement zone (BMZ) antibodies are produced by patients with pemphigoid. In most patients with bullous pemphigoid, serum contains IgG anti-BMZ antibodies, while in cicatricial pemphigoid circulating IgG anti-BMZ antibodies are found in a minority of cases. Sensitivity of detection of anti-BMZ antibodies is increased when serum is tested using sodium chloride (NaCl)-split human skin as substrate. Circulating IgG anti-BMZ antibodies are also detected in patients with epidermolysis bullosa acquisita (EBA) and bullous eruption of lupus erythematosus. IgG anti-cell surface (CS) antibodies are produced by patients with pemphigus. The titer of anti-CS antibodies generally correlates with disease activity of pemphigus. See Method Description for special information pertaining to Herpes gestationis (pemphigoid) and paraneoplastic pemphigus.

CIFS 8052
Useful For: Confirming a diagnosis of pemphigoid, pemphigus, epidermolysis bullosa acquisita, or bullous lupus erythematosus Monitoring therapeutic response in patients with pemphigus

Interpretation: Indirect immunofluorescence (IF) testing may be diagnostic when histologic or direct IF studies are only suggestive, nonspecific, or negative. Anti-cell surface (CS) antibodies correlate with a diagnosis of pemphigus. Anti-basement zone (BMZ) antibodies correlate with a diagnosis of bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita (EBA), or bullous eruption of lupus erythematosus (LE). If serum contains anti-BMZ antibodies, the pattern of fluorescence on sodium chloride(NaCl)-split skin substrate helps distinguish pemphigoid from EBA and bullous LE. Staining of the roof (epidermal side) or both epidermal and dermal sides of NaCl-split skin correlates with the diagnosis of pemphigoid, while fluorescence localized only to the dermal side of the split-skin substrate correlates with either EBA or bullous LE.

Reference Values:
Report includes presence and titer of circulating antibodies. If serum contains BMZ antibodies on split-skin substrate, patterns will be reported as: 1) epidermal pattern, consistent with pemphigoid or 2) dermal pattern, consistent with epidermolysis bullosa acquisita.

Negative in normal individuals. See Results of IF Testing* in Cutaneous Immunofluorescence Testing in Special Instructions.

Clinical References:

Cutaneous Immunofluorescence, Biopsy

Clinical Information: Skin or mucosal tissue from patients with autoimmune bullous diseases, connective tissue disease, vasculitis, lichen planus, and other inflammatory conditions often contains bound immunoglobulin, complement, and/or fibrinogen. Biopsy specimens are examined for the presence of bound IgG, IgM, IgA, third component of complement (C3), and fibrinogen.

Useful For: Confirming a diagnosis of bullous pemphigoid, cicatricial pemphigoid, variants of pemphigoid, all types of pemphigus, dermatitis herpetiformis, linear IgA bullous dermatosis, chronic bullous disease of childhood, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous eruption of lupus erythematosus, herpes gestationis, and atypical or mixed forms of bullous disease, systemic lupus erythematosus, discoid lupus erythematosus, or other variants, vasculitis, lichen planus, and other inflammatory diseases.

Interpretation: In pemphigus, direct immunofluorescence (IF) testing will show deposition of IgG, or rarely IgA, and often complement C3 (C3) at the cell surface (intercellular substances). In bullous pemphigoid and cicatricial pemphigoid, direct IF study demonstrates deposition of IgG and C3 at the basement membrane zone (BMZ) in a linear pattern. In cicatricial pemphigoid, a disease uncommonly associated with circulating anti-BMZ antibodies, direct IF testing is particularly useful. Biopsy from patients with dermatitis herpetiformis will show IgA concentrated in dermal papillae and/or in a granular pattern at the BMZ. In lupus erythematosus (LE), there are granular deposits of immunoglobulin and complement at the BMZ ("lupus band"). A lupus band is typically found in lesional skin from patients with a variety of forms of LE; similar findings in biopsies of uninvolved "normal" skin are consistent with systemic LE. Biopsy of early inflammatory purpuric lesions of vasculitis will show immunoglobulins and/or complement in dermal vessels. The diagnostic value of direct IF testing is illustrated in the chart Results of IF Testing under Cutaneous Immunofluorescence Testing in Special Instructions.

Reference Values:
Report includes description and interpretation of staining patterns. See Results of IF Testing in Cutaneous Immunofluorescence Testing in Special Instructions.

Clinical References: Immunopathology of the Skin. Edited by EH Beutner, TP Chorzelski, V
Cyanide, Blood

Clinical Information: Cyanide (hydrocyanic acid, prussic acid) blocks cellular respiration by binding to and inactivating hemoglobin and enzymes such as cytochrome oxidase having prosthetic groups containing ferric iron (Fe+++). Cyanide is metabolized rapidly by the liver where it is converted to thiocyanate. Therapy of hypertensive crisis with nitroprusside (Nipride) results in elevated cyanide blood concentrations, because the cyano function is transferred from nitroprusside to hemoglobin in the red cell. Symptoms of cyanide poisoning include giddiness, hyperpnea, headaches, palpitation, cyanosis, and unconsciousness. Asphyxial convulsions may precede death; death normally ensues within a few minutes to 3 hours, depending upon the dose. As long as the heart continues to beat, there is a chance of saving the patient because effective antidotes are available; treatment with sodium nitrite and sodium thiosulfate can be effective.

Useful For: Monitoring possible exposure to cyanide Establishing cause of death in cyanide exposure

Interpretation: Blood concentrations in the average population are as high as 0.2 mcg/mL, mostly derived from vegetables such as brussel sprouts. Significant contact with cyanide can produce blood concentrations up to 2.0 mcg/mL without side effects. At concentrations of 2.0 to 4.0 mcg/mL, giddiness, headaches, and hyperpnea are evident. Concentrations >5.0 mcg/mL are potentially lethal. Normal concentration: <0.2 mcg/mL Toxic concentration: > or =2.0 mcg/mL

Reference Values:
Normal: <0.2 mcg/mL
Toxic concentration: > or =2.0 mcg/mL

Clinical References: Medical Toxicology, Third edition, Edited by RC Dart. 2004 pp 1162, 1800

Cyanide, Blood

Reference Values:
Normal (unexposed population):
Non-smoker: less than 0.025 mg/L
Smoker: average 0.41 mg/L

Exposed:
Levels of less than 0.2 mg/L have been found to be non-toxic; however, levels of 0.5 to 1.0 mg/L have been associated with tachycardia and flushing.

Toxic:
Levels of 1.0 â€“ 2.5 mg/L have been associated with obtundation, coma and respiratory depression with levels greater than 2.5 mg/L, and death with values greater than 3 mg/L.

Cyclic AMP, Urinary Excretion

Clinical Information: Cyclic AMP functions as an intracellular "second messenger" regulating the activity of intracellular enzymes or proteins in response to a variety of hormones (eg, parathyroid hormone). Urinary cyclic AMP is elevated in about 85% of patients with hyperparathyroidism.

Useful For: The differential diagnosis of hypercalcemia An adjunct to serum parathyroid hormone measurements, especially in the diagnosis of parathyroid hormone resistance states, such as pseudohypoparathyroidism

Interpretation: Urinary cyclic AMP is elevated in about 85% of patients with hyperparathyroidism
and in about 50% of patients with humoral hypercalcemia of malignancy.

Reference Values:
1.3-3.7 nmol/dL of glomerular filtrate


Cyclic Citrullinated Peptide Antibodies, IgG, Serum

Clinical Information: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic joint inflammation that ultimately leads to joint destruction. RA affects approximately 1% of the world’s population. The diagnosis of RA is established primarily on clinical criteria and serologic findings. Historically, rheumatoid factor (RF), which is an antibody specific for the Fc portion of human IgG, has been considered a marker for RA. RF is, in fact, one of the diagnostic criteria for RA that was established by the American College of Rheumatology.(1) Although 50% to 90% of patients with RA are RF-positive, the specificity of the RF test is known to be relatively poor. RF is found in many patients with other autoimmune diseases, infectious diseases and some healthy individuals. Consequently, a search for better diagnostic markers, with improved specificity for RA, ensued. Antiperinuclear factor (APF) and antikeratin antibodies (AKA), identified by immunofluorescence, were found to have a specificity of close to 90% for RA, but testing for these autoantibodies has never become popular. It was subsequently determined that APF and AKA react with the same antigen, specifically a citrullinated form of filaggrin (citrulline is an unusual amino acid formed by posttranslational modification of arginine residues by the enzyme peptidyl arginine deaminase).(2) Recombinant filaggrin fragments, after enzymatic deamination in vitro, react with autoantibodies in RA sera. Synthetic cyclic citrullinated peptide (CCP) variants also react with anti-filaggrin autoantibodies and serve as the substrate for detecting anti-CCP antibodies serologically. Most studies of anti-CCP antibodies demonstrated that these autoantibodies have much improved specificity for RA compared to RF.(3) See Connective Tissue Diseases Cascade (CTDC) in Special Instructions; also see Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

Useful For: Evaluating patients suspected of having rheumatoid arthritis (RA) Differentiating RA from other connective tissue diseases that may present with arthritis

Interpretation: A positive result for cyclic citrullinated peptide (CCP) antibodies indicates a high likelihood of rheumatoid arthritis (RA). A Mayo prospective clinical evaluation of the CCP antibody test showed a diagnostic sensitivity for RA of 78% with fewer than 5% false positive results in healthy controls (see Cautions). CCP antibodies have also been reported in approximately 40% of seronegative RA patients, and, like rheumatoid factor (RF), a positive CCP antibody result indicates an increased likelihood of erosive disease in patients with RA. High levels of CCP antibodies may be useful to identify patients with aggressive disease, but further studies are needed to document this association. The level of CCP antibodies may also correlate with disease activity in RA, but further studies are needed to document this clinical application.

Reference Values:
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-59.9 U (positive)
> or =60.0 U (strong positive)
Reference values apply to all ages.

Cyclobenzaprine (Flexeril)

**Reference Values:**
Reference Range: 10 - 30 ng/mL

Cyclospora Stain

**Clinical Information:** Cyclospora cayetanensis is an apicomplexan protozoan parasite that causes watery diarrhea, anorexia, malaise, and weight loss. The extent of symptoms depends on the age and condition of the host and the infectious dose. The infection is usually self-limited, but symptoms can be severe and prolonged, particularly in immunocompromised patients. Cyclospora diarrheal disease is endemic in many parts of the world, including Asia, India, Southeast Asia, and Latin America. Although most cases of cyclosporiasis have been seen in travelers to developing countries, outbreaks in the United States have been noted due to contaminated fruits and vegetables from Latin America. Transmission is via fecally contaminated food or water. If untreated, symptoms typically last for 10 to 12 weeks, and may follow a relapsing course. The infection usually responds to treatment with a sulfamethoxazole-trimethoprim drug combination. Cyclospora cayetanensis oocysts are traditionally detected by modified acid-fast staining, in which the oocysts stain bright pink-red. However, the modified Safranin stain has been shown to provide increased sensitivity over modified acid-fast method and produces a more rapid result. It is the method used in our laboratory to detect Cyclospora cayetanensis oocysts in fecal sediment. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** The identification of Cyclospora as a cause of infectious gastroenteritis

**Interpretation:** A report of Cyclospora cayetanensis detected indicates the presence of this parasite in the patient's feces.

**Reference Values:**
Negative
If positive, reported as Cyclospora species detected.

**Clinical References:**

Cyclosporine, Blood

**Clinical Information:** Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by CYP3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis. Dose is adjusted initially (up to 2 months posttransplant) to maintain concentrations generally between 150 and 400 ng/mL. Target trough concentrations vary according to clinical protocol and depend on type of allograft, risk of rejection, concomitant immunosuppressive drugs, and toxicity. After the first 2 postoperative months, the target range is generally lower, between 75 and 300 ng/mL. Conversion between formulations is generally done at the same dose but with drug monitoring.
**Useful For:** Monitoring whole blood cyclosporine concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers. Adjusting dose to optimize immunosuppression while minimizing toxicity. Evaluating patient compliance.

**Interpretation:** Most individuals display optimal response to cyclosporine with trough whole blood levels 100 to 400 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next scheduled dose). Blood drawn at other times will yield higher results. This test may also be used to analyze cyclosporine levels 2 hours after dosing (C2 concentrations); trough therapeutic ranges do not apply to C2 specimens. The assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**
100-400 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.


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**3A5B 63037**

**CYP3A5 Genotype, Blood**

**Clinical Information:** CYP3A5 is 1 of the 4 CYP3 genes localized in tandem on chromosome 7 that encode the CYP3A subfamily of enzymes responsible for the metabolism of more than 50% of medications. CYP3A5 is expressed in liver, as well as extrahepatic tissue such as small intestine, lung, kidney, breast, and prostate. The CYP3A5 expression level and enzymatic activity can be modulated by genetic variation. CYP3A5 allelic frequency depends upon ethnicity. For example, in individuals of European descent the most common allele is the CYP3A5*3 allele (c.219-237A->G), which results in a splicing defect and absence of enzyme activity. In individuals of African descent, the *1 allele (functional enzyme) is most common. The distribution of CYP3A5*3 allele frequencies ranges from 0.14 among sub-Saharan Africans to 0.95 in European populations. In general, most drugs metabolized by CYP3A5 are also metabolized by CYP3A4, with few exceptions. For this reason, substrates of these two enzymes are listed together in most publications and genotyping of both genes might be needed to fully understand the metabolism of these drugs and predict phenotype. The clinical relevance of CYP3A4 and CYP3A5 activity on drug metabolism has not been fully explored in many cases. Tacrolimus is an immunosuppressive calcineurin inhibitor used in transplant recipients. Tacrolimus has a low therapeutic index with a wide range of side effects and large interindividual variability in its pharmacokinetics, particularly in the dose required to reach target trough blood concentrations, thus necessitating routine therapeutic drug monitoring in clinical practice. Tacrolimus dose requirements are closely associated with CYP3A5 genotype. According to existing literature and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, individuals with at least 1 copy of fully functional CYP3A5 (ie, *1/*1 and *1/*3) typically require a higher dose of tacrolimus to reach the targeted whole blood concentrations than those without a copy of a fully functional CYP3A5 allele (ie, *3/*3). CYP3A5*3 genotyping may predict dose requirements for tacrolimus but does not replace the need for therapeutic monitoring to guide tacrolimus dose adjustments. For a patient with the CYP3A5*3/*3 genotype, initiating tacrolimus therapy with a standard (normal) dose is recommended.

**Useful For:** An aid to optimizing treatment with tacrolimus and potentially other drugs metabolized by...
CYP3A5

**Interpretation:** Absence of the *3 allele does not rule out the possibility that a patient harbors another variant that can impact the function of this enzyme, drug response, or drug side effects. CYP3A5 genotype is only one factor that should be taken into consideration for drug dosing. CYP3A5*1/*1

**Extensive (normal) metabolizer:** The CYP3A5*3 allele was not detected. Therefore, this patient is expected to be an extensive (normal) metabolizer. This phenotype is also known as CYP3A5 expresser. Rapid metabolism of drugs that are inactivated or activated by CYP3A5 is expected. Patients with this phenotype should not be co-administered CYP3A5 inhibitors due to an increased risk of toxicity or lack of efficacy, respectively. For patients taking tacrolimus with this genotype, the literature indicates that higher doses may be required, presumably because original dosing guidelines were determined on patients who were poor metabolizers. Therapeutic drug monitoring is recommended.

**CYP3A5*1/*3 Intermediate metabolizer:** One copy of the CYP3A5*3 allele was detected. Therefore, this patient is expected to be an intermediate metabolizer. This phenotype is also known as CYP3A5 expresser. Reduced metabolism of drugs that are inactivated or activated by CYP3A5 is expected when compared to patients who are *1/*1. Patients with this phenotype should not be coadministered CYP3A5 inhibitors due to an increased risk of toxicity or lack of efficacy, respectively. For patients taking tacrolimus with this genotype, the literature indicates that higher doses may be required, presumably because original dosing guidelines were determined on patients who were poor metabolizers like this patient. Therapeutic drug monitoring is recommended. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CYP3A5 Genotype, Saliva**

**Clinical Information:** CYP3A5 is 1 of the 4 CYP genes localized in tandem on chromosome 7 that encode the CYP3A subfamily of enzymes responsible for the metabolism of more than 50% of medications. CYP3A5 is expressed in liver, as well as extrahepatic tissue such as small intestine, lung, kidney, breast, and prostate. The CYP3A5 expression level and enzymatic activity can be modulated by genetic variation. CYP3A5 allelic frequency depends upon ethnicity. For example, in individuals of European descent the most common allele is the CYP3A5*3 allele (c.219-237A>G), which results in a splicing defect and absence of enzyme activity. In individuals of African descent, the *1 allele (functional enzyme) is most common. The distribution of CYP3A5*3 allele frequencies ranges from 0.14 among sub-Saharan Africans to 0.95 in European populations. In general, most drugs metabolized by CYP3A5 are also metabolized by CYP3A4, with few exceptions. For this reason, substrates of these 2 enzymes are listed together in most publications and genotyping of both genes might be needed to fully understand the metabolism of these drugs and predict phenotype. The clinical relevance of CYP3A4 and CYP3A5 activity on drug metabolism has not been fully explored in many cases. Tacrolimus is an immunosuppressive calcineurin inhibitor used in transplant recipients. Tacrolimus has a low therapeutic
index with a wide range of side effects and large interindividual variability in its pharmacokinetics, particularly in the dose required to reach target trough blood concentrations, thus necessitating routine therapeutic drug monitoring in clinical practice. Tacrolimus dose requirements are closely associated with CYP3A5 genotype. Broadly accepted dosing algorithms for use of genotype in dosing of tacrolimus have not been published, although the results of research conducted by Thervet et al(1) provide some guidance on initial dosing. According to existing literature, individuals with at least 1 copy of fully functional CYP3A5 (ie, *1/*1 and *1/*3) typically require a higher dose of tacrolimus to reach the targeted whole blood concentrations than those without a copy of a fully functional CYP3A5 allele (ie, *3/*3). CYP3A5*3 genotyping may predict dose requirements for tacrolimus but does not replace the need for therapeutic monitoring to guide tacrolimus dose adjustments. For a patient with the CYP3A5*3/*3 genotype, initiating tacrolimus therapy with a standard (normal) dose is recommended.

**Useful For:** An aid to optimizing treatment with tacrolimus and potentially other drugs metabolized by CYP3A5 Genotyping patients who prefer not to have venipuncture done

**Interpretation:** Absence of the *3 allele does not rule out the possibility that a patient harbors another variant that can impact the function of this enzyme, drug response, or drug side effects. CYP3A5 genotype is only one factor that should be taken into consideration for drug dosing. CYP3A5*1/*1 Extensive (normal) metabolizer: The CYP3A5*3 allele was not detected. Therefore, this patient is expected to be an extensive (normal) metabolizer. This phenotype is also known as CYP3A5 expresser. Rapid metabolism of drugs that are inactivated or activated by CYP3A5 is expected. Patients with this phenotype should not be coadministered CYP3A5 inhibitors due to an increased risk of toxicity or lack of efficacy, respectively. For patients taking tacrolimus with this genotype, the literature indicates that higher doses may be required, presumably because original dosing guidelines were determined on patients who were poor metabolizers. Therapeutic drug monitoring is recommended. CYP3A5*1/*3 Intermediate metabolizer: One copy of the CYP3A5*3 allele was detected. Therefore, this patient is expected to be an intermediate metabolizer. This phenotype is also known as CYP3A5 expresser. Reduced metabolism of drugs that are inactivated or activated by CYP3A5 is expected when compared to patients who are *1/*1. Patients with this phenotype should not be coadministered CYP3A5 inhibitors due to an increased risk of toxicity or lack of efficacy, respectively. For patients taking tacrolimus with this genotype, the literature indicates that higher doses may be required, presumably because original dosing guidelines were determined on patients who were poor metabolizers. Therapeutic drug monitoring is recommended. CYP3A5*3/*3 Poor metabolizer: Two copies of the CYP3A5*3 allele were detected. Therefore, this patient is expected to be a poor metabolizer. This phenotype is also known as CYP3A5 nonexpresser. Drugs that are inactivated or activated by CYP3A5 are metabolized at greatly reduced rate when compared to patients who are *1/*1. Patients with this phenotype should not be coadministered CYP3A5 inhibitors due to an increased risk of toxicity or lack of efficacy, respectively. For patients taking tacrolimus with this genotype, the literature supports normal dosing, presumably because original dosing guidelines were determined on patients who were poor metabolizers like this patient. Therapeutic drug monitoring is recommended. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Since it is formed at a constant rate and freely filtered by the kidneys, its serum concentration is inversely correlated with the glomerular filtration rate (GFR); that is, high values indicate low GFRs while lower values indicate higher GFRs, similar to creatinine. The renal handling of cystatin C differs from creatinine. While both are freely filtered by glomeruli, once it is filtered, cystatin C, unlike creatinine, is reabsorbed and metabolized by proximal renal tubules. Thus, under normal conditions, cystatin C does not enter the final excreted urine to any significant degree. The serum concentration of cystatin C remains unchanged with infections, inflammatory or neoplastic states, and is not affected by body mass, diet, or drugs. Thus, cystatin C may be a more reliable marker of renal function (GFR) than creatinine. Estimated Glomerular Filtration Rate (GFR): GFR can be estimated (eGFR) from serum cystatin C utilizing an equation which includes the age and gender of the patient. The CKD-EPI cystatin C equation was developed by Inker et al(1) and demonstrated good correlation with measured iothalamate clearance in patients with all common causes of kidney disease, including kidney transplant recipients. Cystatin C eGFR may have advantages over creatinine eGFR in certain patient groups in whom muscle mass is abnormally high or low (for example quadriplegics, very elderly, or malnourished individuals). Blood levels of cystatin C also equilibrate more quickly than creatinine, and therefore, serum cystatin C may be more accurate than serum creatinine when kidney function is rapidly changing (for example amongst hospitalized individuals).

**Useful For:**
Cystatin C: An index of glomerular filtration rate, especially in patients where serum creatinine may be misleading (eg, very obese, elderly, or malnourished patients) Assessing renal function in patients suspected of having kidney disease Monitoring treatment response in patients with kidney disease Estimated Glomerular Filtration Rate (eGFR): An index of GFR, especially in patients where serum creatinine may be misleading (eg, very obese, elderly, or malnourished patients); for such patients, use of CKD-EPI cystatin C equation is recommended to estimate GFR Assessing renal function in patients suspected of having kidney disease Monitoring treatment response in patients with kidney disease

**Interpretation:**
Cystatin C inversely correlates with the glomerular filtration rate (GFR), that is elevated levels of cystatin C indicate decreased GFR. Cystatin C may provide more accurate assessment of GFR for very obese, elderly, or malnourished patients than creatinine. Cystatin C equation does not require patient ethnic data, and can be used for those patients with this information unavailable. Due to immaturity of renal function, cystatin C levels are higher in neonates <3 months of age.(2) Chronic kidney disease (CKD) is defined as the presence of: persistent and usually progressive reduction in GFR (GFR <60 mL/min/1.73 m[2]) and/or albuminuria (>30 mg of urinary albumin per gram of urinary creatinine), regardless of GFR. According to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) classification, among patients with CKD, irrespective of diagnosis, the stage of disease should be assigned based on the level of kidney function: Stage Description GFR mL/min/BSA 1 Kidney damage with normal or increased GFR 90-120 2 Kidney damage with mild decrease in GFR 60-89 3 Moderate decrease in GFR 30-59 4 Severe decrease in GFR 15-29 5 Kidney failure <15 (or dialysis)

**Reference Values:**

**CYSTATIN C**

**Males:**
- 0 days-22 years: no reference values established
- 23-29 years: 0.60-1.03 mg/L
- 30-39 years: 0.64-1.12 mg/L
- 40-49 years: 0.68-1.22 mg/L
- 50-59 years: 0.72-1.32 mg/L
- 60-69 years: 0.77-1.42 mg/L
- 70-79 years: 0.82-1.52 mg/L
- >79 years: no reference values established

**Females:**
- 0 days-22 years: no reference values established
- 23-29 years: 0.57-0.90 mg/L
- 30-39 years: 0.59-0.98 mg/L
- 40-49 years: 0.62-1.07 mg/L
- 50-59 years: 0.64-1.17 mg/L
- 60-69 years: 0.66-1.26 mg/L
- 70-80 years: 0.68-1.36 mg/L
81-86 years: 0.70-1.45 mg/L
>86 years: no reference values established

eGFR
>60 mL/min/BSA
eGFR will not be calculated for patients under 18 years.


Cystic Fibrosis Mutation Analysis, 106-Mutation Panel

Clinical Information: Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. The incidence of CF varies markedly among different populations, as does the mutation detection rate for the mutation screening assay. To date, over 1,500 mutations have been described within the CF gene, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, deltaF508, accounts for approximately 67% of the mutations worldwide and approximately 70% to 75% in a North American Caucasian population. Most of the remaining mutations are rather rare, although some show a relatively higher prevalence in certain ethnic groups or in some atypical presentations of CF such as congenital bilateral absence of the vas deferens (CBAVD). Mutations detected by the assay performed in the Mayo Clinic Molecular Genetics Laboratory include the 23 mutations recommended by the American College of Medical Genetics as well as 83 other mutations. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least 1 copy of the G178R, G551S, G551D, S549N, S549R, G1244E, S1251N, S1255P, or G1349D mutation. The G178R, S549N, S549R, S551D, and S1251N mutations are included in this test. These 106 mutations account for approximately 91% of CF chromosomes in a Northern European Caucasian population. Detection rates for several ethnic and racial groups are listed in the table below. Note that interpretation of test results and risk calculations are also dependent on clinical information and family history. Racial or Ethnic Group Carrier Frequency Mutation Detection Rate* African American 1/65 81% Ashkenazi Jewish 1/25 97% Asian American (excluding individuals of Japanese ancestry) 1/90 54% Mixed European 1/25 82% Eastern European 1/25 77% French Canadian 1/25 91% Hispanic American 1/46 82% Northern European 1/25 91% Southern European 1/25 79% *Rates are for classical CF. Rates are lower for atypical forms of CF and for CBAVD. CFTR mutations listed below are included in this panel. Deletion exons 2-3 Exon 11: R553X Intron 2: 296+2 T->A Exon 11: A559T Exon 3: E60X Exon 11: R560T Exon 3: R75X Intron 11: 1811+1.6kb A->G Exon 3: G85E Intron 11: 1812-1 G->A Exon 3: 394_395delTT Intron 12: 1898+1 G->A Exon 4: 444delA Exon 12: P574H Exon 4: 457TAT->G Exon 13: 1949del84 Exon 4: R117H Exon 13: 2043delG Exon 4: R117C Exon 13: 2055del9->A Exon 4: Y122X Exon 13: 2105del13ins5 Exon 4: 574delA Exon 13: 2108delA Intron 4: 621+1 G->A Exon 13: 2143delT Exon 5: 663delT Exon 13: 2183_2184delAinsG Exon 5:
**Useful For:** Confirmation of a clinical diagnosis of cystic fibrosis Risk refinement via carrier screening for individuals in the general population Prenatal diagnosis or familial mutation testing when the familial mutations are included in the 106-mutation panel listed above (if familial mutations are not included in the 106-mutation panel, order FMTT / Familial Mutation, Targeted Testing) Risk refinement via carrier screening for individuals with a family history when familial mutations are not available Identification of patients who may respond to CFTR potentiator therapy

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Cysticercosis Antibody, IgG by ELISA**

**Interpretation:** Seroconversion between acute and convalescent sera is considered strong evidence of recent infection. The best evidence for infection is a significant change on two appropriately timed specimens where both tests are done in the same laboratory at the same time. Patients with collagen vascular diseases, hepatic cirrhosis, schistosomiasis, and other parasitic infections can produce false-positive results. There is a strong cross-reaction between cysticercosis and echinococcosis positive sera. Confirmation of positive ELISA results by the cysticercosis antibody, IgG by Western blot is recommended.

**Reference Values:**
Reference Interval: <=0.34 O.D.

0.34 O.D. or less: Negative- No significant level of cysticercosis IgG antibody detected.

0.35-0.50 O.D.: Equivocal- Questionable presence of cysticercosis IgG antibody detected.
Repeat testing in 10-14 days may be helpful.

0.51 O.D. or greater: Positive- IgG antibody to cysticercosis detected, which may suggest current or past infection.

**Cysticercus Antibody, ELISA (CSF)**

**Reference Values:**
Reference Range: <0.75

**Interpretive Criteria:**

\[
< 0.75 \quad \text{Antibody Not Detected} \\
\geq 0.75 \quad \text{Antibody Detected}
\]

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps.

Antibodies to other parasitic infections, particularly echinococcosis, may crossreact in the cysticercus IgG ELISA. Confirmation of positive ELISA results by the cysticercus IgG antibody Western blot is thus recommended.

**Cystinuria Profile, Quantitative, 24 Hour, Urine**

**Clinical Information:** Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestine and in the kidney. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7,000. Cystinuria can be classified into 3 subtypes based on the excretion of amino acids in the urine of heterozygotes (parents or children of affected individuals). Heterozygotes of type I excrete normal amounts of cystine, while those with types II and III present with slight to moderate excretion of cystine and other amino acids (lysine, arginine, and ornithine). All 3 subtypes are caused by mutations in only 2 genes, SLC3A1 on chromosome 2p and SLC7A9 on chromosome 19q. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to mutations in the SLC3A1 gene; type B, due to mutations in the SLC7A9 gene; and type AB, due to 1 mutation in each SLC3A1 and SLC7A9.

**Useful For:** Diagnosis of cystinuria

**Interpretation:** Homozygotes or compound heterozygotes with cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) are also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for non-type I cystinuria can be distinguished by the pattern of urinary amino acids excretion: the former secretes large amounts of cystine and all 3 dibasic amino acids, whereas the latter secretes more lysine and cystine than arginine and ornithine.

**Reference Values:**

**CYSTINE**

3-15 years: 11-53 mcmol/24 hours
> or ≥16 years: 28-115 mc mol/24 hours

LYSINE
3-15 years: 19-140 mc mol/24 hours
> or ≥16 years: 32-290 mc mol/24 hours

ORNITHINE
3-15 years: 3-16 mc mol/24 hours
> or ≥16 years: 5-70 mc mol/24 hours

ARGININE
3-15 years: 10-25 mc mol/24 hours
> or ≥16 years: 13-64 mc mol/24 hours

Conversion Formulas:
Result in mc mol/24 hours x 0.24 = result in mg/24 hours
Result in mg/24 hours x 4.17 = result in mc mol/24 hours


Cystinuria Profile, Quantitative, Random, Urine

Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestine and in the kidney. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7,000. Cystinuria can be classified into 3 subtypes based on the excretion of amino acids in the urine of heterozygotes (parents or children of affected individuals). Heterozygotes of type I excrete normal amounts of cystine, while those with types II and III present with slight to moderate excretion of cystine and other amino acids (lysine, arginine, and ornithine). All 3 subtypes are caused by mutations in only 2 genes, SLC3A1 on chromosome 2p and SLC7A9 on chromosome 19q. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to mutations in the SLC3A1 gene; type B, due to mutations in the SLC7A9 gene; and type AB, due to 1 mutation in each SLC3A1 and SLC7A9.

Useful For: Biochemical diagnosis and monitoring of cystinuria

Interpretation: Homozygotes or compound heterozygotes with cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) is also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for non-type I cystinuria can be distinguished by the pattern of urinary amino acids excretion: homozygous individuals secrete large amounts of cystine and all 3 dibasic amino acids, whereas heterozygous individuals secrete more lysine and cystine than arginine and ornithine.

Reference Values:

<table>
<thead>
<tr>
<th>Urine Amino Acid</th>
<th>Age Groups</th>
<th>&lt; or =12 Months</th>
<th>13-35 Months</th>
<th>3-6 Years</th>
<th>7-8 Years</th>
<th>9-17 Years</th>
<th>&gt; or ≥18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=36)</td>
<td>(n=45)</td>
<td>(n=39)</td>
<td>(n=10)</td>
<td>(n=40)</td>
<td>(n=145)</td>
<td></td>
</tr>
<tr>
<td>Reference Values</td>
<td>(nmol/mg creatinine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arginine  Arg  10-560  20-395  14-240
Ornithine  Orn
Cystine  Cys  12-504  11-133  10-98


Cytochrome Oxidase Stain (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

Cytochrome P450 1A2 Genotype
Clinical Information: The cytochrome P450 (CYP) family is involved in the primary metabolism of many drugs. The CYPs are a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs. CYP1A2-mediated drug metabolism is highly variable. A number of variants have been identified in the CYP1A2 gene that result in increased, diminished, or abolished catalytic activity and substrate metabolism. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the CYP1A2 genotype. Individuals who are poor metabolizers may require lower than usual doses to achieve optimal response, whereas individuals who are ultrarapid metabolizers may benefit from increased doses. CYP1A2 phenotype is predicted based upon the number of functional, partially functional, nonfunctional, and inducible alleles present in a sample. In the absence of clear guidance on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism also may benefit by switching to another comparable drug that is not primarily metabolized by CYP1A2 or by therapeutic drug monitoring where applicable. The following table outlines the relationship between the variations (star alleles) detected in this assay and the effect on the activity of the enzyme produced by that allele.

<table>
<thead>
<tr>
<th>CYP1A2 Allele</th>
<th>Nucleotide Change* (Legacy nomenclature)*</th>
<th>cDNA Nucleotide Change Effect on Enzyme Metabolism**</th>
<th>*1 None (wild type)</th>
<th>*1K -729C-&gt;T c.-10+113C-&gt;T Decreased activity and decreased inducibility</th>
<th>*1F -163C-&gt;A c.-9-154C-&gt;A Increased inducibility</th>
<th>*4 2499A-&gt;T c.1156A-&gt;T Greatly reduced activity</th>
<th>*5 3497G-&gt;A c.1217G-&gt;A Decreased activity</th>
<th>*6 5090C-&gt;T c.1291C-&gt;T No activity</th>
<th>*7 3533G-&gt;A c.1253+1G-&gt;A No activity</th>
<th>*8 5166G-&gt;A c.1367G-&gt;A No activity</th>
<th>*11 558C-&gt;A c.558C-&gt;A No activity</th>
<th>*15 125C-&gt;G c.125C-&gt;G No activity</th>
<th>*16 2473G-&gt;A c.1130G-&gt;A No activity **The frequency of these variants varies by ethnicity.</th>
</tr>
</thead>
</table>

*Effect of a specific allele on the activity of the CYP1A2 enzyme can only be estimated since the literature does not provide precise data. A complicating factor in correlating CYP1A2 genotype to CYP1A2 phenotype is that some drugs or their metabolites are inhibitors of CYP1A2 catalytic activity. These drugs may reduce CYP1A2 catalytic activity. Consequently, an individual may require a dose decrease greater than predicted based upon genotype alone. Another complicating factor is that CYP1A2 is inducible by several drugs and environmental agents (eg, cigarette smoke) and the degree of inducibility is under genetic control. It is important to interpret the results of testing in the context of other coadministered drugs and environmental factors.
Useful For: Identifying individuals who are poor, intermediate, extensive, or ultrarapid metabolizers of drugs metabolized by CYP1A2 to assist drug therapy decision making

Interpretation: An interpretive report will be provided that includes assay information, genotype, and an interpretation indicating whether results are consistent with a poor, intermediate, extensive, or ultrarapid metabolizer phenotype. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(1) CYP1A2 activity is also dependent upon hepatic function status, as well as age. Renal function may be important for drugs that are also excreted in urine. Patients may develop drug toxicity if hepatic or renal function is decreased. Drug metabolism is known to decrease with age. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and age. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References:

Cytochrome P450 1A2 Genotype, Saliva

Clinical Information: The cytochrome P450 (CYP) family is involved in the primary metabolism of many drugs. The CYPs are a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs. CYP1A2-mediated drug metabolism is highly variable. A number of variants have been identified in the CYP1A2 gene that results in increased, diminished, or abolished catalytic activity and substrate metabolism. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the CYP1A2 genotype. Individuals who are poor metabolizers may require lower than usual doses to achieve optimal response, whereas individuals who are ultrarapid metabolizers may benefit from increased doses. CYP1A2 phenotype is predicted based upon the number of functional, partially functional, nonfunctional, and inducible alleles present in a sample. In the absence of clear guidance on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism also may benefit by switching to another comparable drug that is not primarily metabolized by CYP1A2 or by therapeutic drug monitoring where applicable. The following table outlines the relationship between the variations (star alleles) detected in this assay and the effect on the activity of the enzyme produced by that allele.

<table>
<thead>
<tr>
<th>CYP1A2 Allele Nucleotide Change* (Legacy nomenclature)*</th>
<th>cDNA Nucleotide Change Effect on Enzyme Metabolism**</th>
<th>*1 None (wild type)</th>
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<th>metabolizer</th>
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<tbody>
<tr>
<td>*1K -729C-&gt;T</td>
<td>c.-10+113C-&gt;T Decreased activity and decreased inducibility</td>
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<td>*4 2499A-&gt;T c.1156A-&gt;T Greatly reduced activity</td>
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</tr>
</tbody>
</table>
| *7 3533G->A c.1253+1G->A No activity | *8 5166G->A c.1367G->A No activity | *11 558C->A c.558C->A No activity | *15 125C->G c.125C->G No activity | *16 2473G->A c.1130G->A No activity **The frequency of these variants varies by ethnicity. *Effect of a specific allele on the activity of the CYP1A2 enzyme can only be estimated since the literature does not provide precise data. A complicating factor in correlating CYP1A2 genotype to CYP1A2 phenotype is that some drugs or their metabolites are inhibitors of CYP1A2 catalytic activity. These drugs may reduce CYP1A2 catalytic activity. Consequently, an individual may require a dose decrease greater than predicted based upon genotype alone. Another complicating factor is that CYP1A2 catalytic activity is also dependent upon hepatic function status, as well as age. Renal function may be important for drugs that are also excreted in urine. Patients may develop drug toxicity if hepatic or renal function is decreased. Drug metabolism is known to decrease with age. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and age. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.
is inducible by several drugs and environmental agents (eg, cigarette smoke) and the degree of inducibility is under genetic control. It is important to interpret the results of testing in the context of other coadministered drugs and environmental factors.

**Useful For:** Identifying individuals who are poor, intermediate, extensive, or ultrarapid metabolizers of drugs metabolized by CYP1A2 to assist drug therapy decision making Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report will be provided that includes assay information, genotype, and an interpretation indicating whether results are consistent with a poor, intermediate, extensive, or ultra-rapid metabolizer phenotype. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(1) CYP1A2 activity is also dependent upon hepatic function status, as well as age. Renal function may be important for drugs that are also excreted in urine. Patients may develop drug toxicity if hepatic or renal function is decreased. Drug metabolism is known to decrease with age. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and age. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Cytochrome P450 2C19 Genotype, Blood**

**Clinical Information:** Primary metabolism of many drugs is performed by cytochrome P450 (CYP450) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C19, participates in the metabolism of a wide variety of drugs, including the activation of the anticoagulant clopidogrel, and the inactivation of citalopram. CYP2C19 drug metabolism is variable among individuals. Some individuals have CYP2C19 genetic variants that lead to severely diminished or absent CYP2C19 catalytic activity (ie, poor metabolizers). The frequency of CYP2C19 variants (also referred to as polymorphisms) depends on ethnicity. CYP2C19 variants that produce poor metabolizers are found with frequencies of 2% to 5% in Caucasians, 4% in African Americans, 13% to 23% in Asians, and 38% to 79% in Polynesians and Micronesians. The following table displays the CYP2C19 variants detected by this assay, the corresponding star allele, and the effect on CYP2C19 enzyme activity: CYP2C19 Allele Nucleotide Change Effect on Enzyme Activity *1 None (wild type) Extensive metabolizer (normal) *2 c.681G>A No activity *3 c.636G>A No activity *4 c.1A>G No activity *5 c.1297C>T No activity *6 c.395G>A No activity *7 c.819+2T>A No activity *8 c.358T>C Severely decreased *9 c.431G>A Decreased *10 c.680C>T Severely decreased *17 c.-806C>T Enhanced activity CYP2C19 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19 *1/*1. If an individual is homozygous or compound heterozygous for an alleles with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. Individuals with the CYP2C19*17 allele (in the absence of any inactive or decreased activity alleles) may have enhanced metabolism of drugs. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit...
from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C19. It is important to interpret the results of testing in the context of other coadministered drugs.

**Useful For:** Identifying patients who may be at risk for altered metabolism of drugs that are modified by CYP2C19 Predicting anticoagulation response to clopidogrel

**Interpretation:** A report will be provided that includes CYP2C19 genotype, predicted CYP2C19 phenotype, and assay information. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered when treating intermediate metabolizers. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**2C19C 62997**

**Cytochrome P450 2C19 Genotype, Saliva**

**Clinical Information:**
Primary metabolism of many drugs is performed by cytochrome P450 (CYP450) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C19, participates in the metabolism of a wide variety of drugs, including the activation of the anticoagulant clopidogrel, and the inactivation of citalopram. CYP2C19 drug metabolism is variable among individuals. Some individuals have CYP2C19 genetic variants that lead to severely diminished or absent CYP2C19 catalytic activity (ie, poor metabolizers). The frequency of CYP2C19 variants (also referred to as polymorphisms) depends on ethnicity. CYP2C19 variants that produce poor metabolizers are found with frequencies of 2% to 5% in Caucasians, 4% in African Americans, 13% to 23% in Asians, and 38% to 79% in Polynesians and Micronesians. The following table displays the CYP2C19 variants detected by this assay, the corresponding star allele, and the effect on CYP2C19 enzyme activity; CYP2C19 Allele Nucleotide Change Effect on Enzyme Metabolism *1 None (wild type) Extensive metabolizer (normal) *2 c.681G->A No activity *3 c.636G->A No activity *4 c.1A->G No activity *5 c.1297C->T No activity *6 c.395G->A No activity *7 c.819+2T->A No activity *8 c.358T->C Severely decreased *9 c.431G->A Decreased *10 c.680C>TG Severely decreased *17 c.-806C->T Enhanced activity CYP2C19 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19 *1/*1. If an individual is homozygous or compound heterozygous for an allele(s) with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. Individuals with the CYP2C19*17 allele (in the absence of any inactive or decreased activity alleles) may have enhanced metabolism of drugs. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C19. It is important to interpret the results of testing in the context of other coadministered drugs.
Useful For: Identifying patients who may be at risk for altered metabolism of drugs that are modified by CYP2C19
Predicting anticoagulation response to clopidogrel
Genotyping patients who prefer not to have venipuncture done

Interpretation: A report will be provided that includes CYP2C19 genotype, predicted CYP2C19 phenotype, and assay information. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered when treating intermediate metabolizers. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.

Clinical References:

2C9B
36441

Cytochrome P450 2C9 Genotype by Sequence Analysis, Blood

Clinical Information: Primary metabolism of many drugs is performed by cytochrome P450 (CYP450), a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C9, participates in the metabolism of a wide variety of drugs including warfarin and phenytoin. CYP2C9-mediated drug metabolism is variable among individuals. Some individuals have CYP2C9 genetic variants that lead to severely diminished or absent CYP2C9 catalytic activity (ie, poor metabolizers). These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. A number of specific CYP2C9 variants have been identified that result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in the assay and their effect on enzyme activity: CYP2C9 Allele cDNA Nucleotide Change Effect on Enzyme Metabolism *1 None (wild type) Extensive metabolizer (normal) *2 430C->T Reduced activity *3 1075A->C No activity *4 1076T->C Reduced activity *5 1080C->G Reduced activity *6 818delA No activity *8 449G->A Substrate specific *9 752A->G Reduced activity *11 1003C->T Reduced activity CYP2C9 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19 *1/*1. If an individual is homozygous or compound heterozygous for an allele with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C9. It is important to interpret the results of testing in the context of other coadministered drugs.

Useful For: Identifying individuals who may be at risk for altered metabolism of drugs that are modified by CYP2C9

Interpretation: A report will be provided that includes CYP2C9 genotype, predicted CYP2C9
phenotype, and assay information. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(1) Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug/metabolite inhibition must be considered in the case of intermediate metabolism. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.

Clinical References:

Cytochrome P450 2C9 Genotype by Sequence Analysis, Saliva

Clinical Information: Primary metabolism of many drugs is performed by cytochrome P450 (CYP450), a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C9, participates in the metabolism of a wide variety of drugs including warfarin and phenytoin. CYP2C9-mediated drug metabolism is variable among individuals. Some individuals have CYP2C9 genetic variants that lead to a severely diminished or absent CYP2C9 catalytic activity (ie, poor metabolizers). These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. A number of specific CYP2C9 variants have been identified that result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in the assay and their effect on enzyme activity: CYP2C9 Allele cDNA Nucleotide Change Effect on Enzyme Metabolism *1 None (wild type) Extensive metabolizer (normal) *2 430C->T Reduced activity *3 1075A->C No activity *4 1076T->C Reduced activity *5 1080C->G Reduced activity *6 818delA No activity *8 449G->A Substrate specific *9 752A->G Reduced activity *11 1003C->T Reduced activity CYP2C9 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19 *1/*1. If an individual is homozygous or compound heterozygous for an allele with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C9. It is important to interpret the results of testing in the context of other coadministered drugs.

Useful For: Identifying individuals who may be at risk for altered metabolism of drugs that are modified by CYP2C9 Genotyping patients who prefer not to have venipuncture done

Interpretation: A report will be provided that includes CYP2C9 genotype, predicted CYP2C9 phenotype, and assay information. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(1) Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For
additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered in the case of intermediate metabolism. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.


**2D6CB**

**Cytochrome P450 2D6 (CYP2D6) Comprehensive Cascade, Blood**

**Clinical Information:** The cytochrome P450 (CYP) family of enzymes is responsible for primary metabolism of many drugs. CYP450s are oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of the CYP enzymes, CYP2D6, is wholly or partially responsible for the metabolism of many commonly prescribed drugs such as some analgesics, anticonvulsants, antidepressants, antipsychotics, antihypertensives, antiestrogens, antineoplastics, antipsychotics, antiretrovirals, antitussives, beta-blockers, cardioactive drugs, H-2 blockers, stimulants, sympathomimetic and other drug classes. The CYP2D6 gene is highly variable with over 100 named alleles. The gene may be deleted, duplicated, and multiplied, and can have multiple sequence variations. In addition, some individuals have genes that are hybrids of CYP2D6 and the CYP2D7 pseudogene. Some individuals have altered CYP2D6 variants that result in synthesis of enzyme devoid of catalytic activity, or an enzyme with diminished catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly depending upon the gene variant found on each chromosome. CYP2D6 duplications and multiplications involving active alleles may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict ultrarapid, ultrarapid to extensive (normal), extensive (normal), extensive (normal) to intermediate, intermediate, intermediate to poor, and poor metabolizer phenotypes. (see Table 1) Table 1. Enzyme Activity of Individual Star Alleles Enzyme Activity Examples of CYP2D6 star alleles Extensive metabolism (normal) *1, *35 Increased activity *2A Decreased activity *2, *9, *10, *14B, *17, *29 and *41 Negligible activity *36 No or null activity *3, *4, *4N, *5, *6, *7, *8, *11, *12, *13, *14A, *15, *68 CYP2D6 phenotype is predicted based upon the number of functional, partially functional, and nonfunctional alleles present in a sample. (see Table 2) Table 2. Phenotype Assignment of CYP2D6 Predicted Drug Metabolizer Phenotype** Without Gene Duplication With Gene Duplication UM 2 increased activity alleles 3 normal and/or increased activity alleles EM to UM A combination of 1 normal activity allele with 1 increased activity allele A combination of 2 normal alleles with one decreased activity allele EM 2 normal activity alleles; a combination of one increased activity allele with one decreased allele A combination of 2 normal alleles with 1 null allele; a combination of 1 normal allele with 2 decreased activity alleles IM to EM A combination of 1 normal activity allele with 1 decreased activity allele; a combination of 1 increased activity with 1 null allele 1 increased activity allele with 2 null alleles, 3 decreased activity alleles IM 1 normal activity allele with 1 null activity allele; 2 decreased activity alleles 1 normal allele with 2 or more null alleles, 2 decreased activity alleles with 1 null allele. PM to IM A combination of 1 decreased activity allele with 1 null allele 1 decreased activity allele with 2 null allele PM Only null alleles detected * Phenotyping was derived from the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website and the PharmGKB website for the related Clinical
Pharmacogenetics Implementation Consortium guidelines. **Ultra-Rapid Metabolizer, UM; Extensive Metabolizer, EM; Intermediate Metabolizer, IM; Poor Metabolizer, PM** There are instances where a phenotype prediction is not categorical and, in these instances, a range of possible phenotypes will be given. It should be noted that other laboratories may use different phenotype prediction methods as there is no consensus on this at this time. However, the method used here represents the findings of the majority of literature available at this time. Individuals without a detectable gene alteration will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2D6 *1/*1. Dosing drugs that are metabolized through CYP2D6 may require adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response in the case of drugs that are inactivated by the CYP2D6 enzyme and higher than usual doses in the case of drugs that are activated by CYP2D6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that are inactivated by CYP2D6 enzyme and lower doses in the case of drugs that are activated by CYP2D6. In the absence of clear guidance from FDA on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit by switching to another comparable drugs that is not primarily metabolized by CYP2D6 or by therapeutic drug monitoring where applicable. Overall, this test provides a comprehensive CYP2D6 genotype result for patients, ensuring a more accurate phenotype prediction. This assay has clinical significance for patients taking or considering medications activated (eg, codeine, tramadol, and tamoxifen) or inactivated (eg, antidepressants and antipsychotics) by the CYP2D6 enzyme. The different tiers associated with the CYP2D6 Cascade will be sequentially initiated until a complete genotype is determined.

**Useful For:** Providing information relevant to tamoxifen, codeine, and tramadol, as well as other medications metabolized by CYP2D6 Determining the exact genotype when other methods fail to generate this information or if genotype-phenotype discord is encountered clinically Identifying exact genotyping when required (eg, drug trials, research protocols) Identifying novel variants that may interfere with drug metabolism

**Interpretation:** A comprehensive interpretive report will be provided that combines the results of all tier testing utilized to obtain the final genotype. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(1) For the CYP2D6 Copy Number Variation assay, the reportable copy number range is 0 to 4 copies for each of the CYP2D6 region assessed. Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
A comprehensive interpretive report will be provided.

**Clinical Information**: The cytochrome P450 (CYP) family of enzymes is responsible for primary metabolism of many drugs. CYP450s are oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of the CYP enzymes, CYP2D6, is wholly or partially responsible for the metabolism of many commonly prescribed drugs such as some analgesics, anticonvulsants, antidepressants, antipsychotics, antiepileptics, antihypertensives, antieosinophils, antineoplastics, antipsychotics, antiretrovirals, antithyroid agents, beta-blockers, cardioactive drugs, H-2 blockers, stimulants, sympathomimetic and other drug classes. The CYP2D6 gene is highly variable with over 100 named alleles. The gene may be deleted, duplicated, and multiplied, and can have multiple sequence variations. In addition, some individuals have genes that are hybrids of CYP2D6 and the CYP2D7 pseudogene. Some individuals have altered CYP2D6 variants that result in synthesis of enzyme devoid of catalytic activity, or an enzyme with diminished catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly depending upon the gene variant found on each chromosome. CYP2D6 duplications and multiplications involving active alleles may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict ultrarapid, ultrarapid to extensive (normal), extensive (normal), extensive (normal) to intermediate, intermediate, intermediate to poor, and poor metabolizer phenotypes for a sample.(see Table 1) Table 1. Enzyme Activity of Individual Star Alleles Enzyme Activity Examples of CYP2D6* alleles Extensive metabolism (normal) *1, *35 Increased activity *2A Decreased activity *2, *9, *10, *14B, *17, *29, *41 No or null activity *3, *4, *4N, *5, *6, *7, *8, *11, *12, *13, *14A, *15 CYP2D6 phenotype is predicted based upon the number of functional, partially functional, and nonfunctional alleles present in a sample.(see Table 2) Table 2. Phenotype Assignment of CYP2D6 Predicted Drug Metabolizer Phenotype** Without Gene Duplication With Gene Duplication UM 2 increased activity alleles 3 normal and/or increased activity alleles EM to UM A combination of 1 normal activity allele with 1 increased activity allele A combination of 2 normal alleles with one decreased activity allele EM 2 normal activity alleles; a combination of one increased activity allele with one decreased allele A combination of 2 normal alleles with 1 null allele; a combination of 1 normal allele with 2 decreased activity alleles IM to EM A combination of 1 normal activity allele with 1 decreased activity allele; a combination of 1 increased activity allele with 1 null allele 1 increased activity allele with 2 null alleles, 3 decreased activity alleles IM 1 normal activity allele with 1 null activity allele; 2 decreased activity alleles 1 normal allele with 2 or more null alleles, 2 decreased activity alleles with 1 null allele. PM to IM A combination of 1 decreased activity allele with 1 null allele 1 decreased activity allele with 2 null allele PM Only null alleles detected * Phenotyping was derived from the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website and the PharmGKB website for the related Clinical Pharmacogenetics Implementation Consortium guidelines. **Ultra-Rapid Metabolizer, UM; Extensive Metabolizer, EM; Intermediate Metabolizer, IM; Poor Metabolizer, PM** There are instances where a phenotype prediction is not categorical and, in these instances, a range of possible phenotypes will be given. It should be noted that other laboratories may use different phenotype prediction methods as there is no consensus on this at this time. However, the method used here represents the findings of the majority of literature available at this time. Individuals without a detectable gene alteration will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2D6 *1/*1. Dosing drugs that are metabolized by CYP2D6 may require adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response in the case of drugs that are inactivated by the CYP2D6 enzyme, and higher than usual doses in the case of drugs that are activated by CYP2D6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that are inactivated by CYP2D6 enzyme, and lower doses in the case of drugs that are activated by CYP2D6. In the absence of clear guidance from FDA on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit from therapeutic drug monitoring or switching to another comparable drug that is not primarily metabolized by CYP2D6.

**Useful For**: Determining the CYP2D6 genotype of patients considered for treatment with tamoxifen, codeine, and tramadol, as well as other medications metabolized by CYP2D6 Genotyping patients who prefer not to have venipuncture done

**Interpretation**: An interpretive report will be provided. All alterations detected will be reported with standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee (http://www.cypalleles.ki.se/CYP2D6.htm). Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic
genes and their associated drugs, please see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.


3A4B

Cytochrome P450 3A4 Genotype, Blood

Clinical Information: The cytochrome P450 (CYP) 3A4 enzyme is responsible for the metabolism of approximately 50% of drugs that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells, including lipid-lowering drugs. The CYP3A4 enzyme activity is highly variable. Interindividual differences in enzyme expression may be due to several factors including: variable homeostatic control mechanisms, disease states that alter homeostasis, up- or down-regulation by environmental stimuli, and genetic variation.(1) A CYP3A4 intron 6 variant, CYP3A4*22 (c.522-191C>T), affects hepatic expression of CYP3A4 and response to statin drugs. The CYP3A4*22 allele is associated with reduced CYP3A4 activity, which may result in a better response to lipid-lowering drugs, such as simvastatin, atorvastatin, or lovastatin. However, reduced CYP3A4 activity may also be associated with statin-induced myopathy, especially for simvastatin. Studies show that in livers with the wild-type genotype (homozygous C or CC) the CYP3A4 mRNA level and enzyme activity were 1.7- and 2.5-fold greater than in heterozygous CYP3A4*22 (CT) and homozygous CYP3A4*22 (TT) carriers, respectively. In 235 patients taking stable doses of drugs for lipid control, carriers of the T allele required significantly lower statin doses for optimal lipid control than did non-T carriers.(2) These results indicate that CYP3A4*22 markedly affects expression of CYP3A4 and could serve as a biomarker for CYP3A4 metabolizer phenotype. The reported allele frequency of CYP3A4*22 in Caucasians is 5% to 8%. The allele frequency is 4.3% in African Americans and in Chinese. Individuals without a detectable CYP3A4*22 variant, will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP3A4*1/*1.

Useful For: Aids in determining therapeutic strategies for drugs that are metabolized by CYP3A4, including atorvastatin, simvastatin, and lovastatin

Interpretation: Extensive metabolizer: The CYP3A4*22 allele was not detected. Therefore, this patient is expected to be an extensive metabolizer. Rapid metabolism of drugs that are inactivated or activated by CYP3A4 is expected. Coadministration of CYP3A4 inhibitors may increase the risk of toxicity for drugs inactivated by CYP3A4, or may cause lack of efficacy for drugs activated by CYP3A4. Intermediate to extensive metabolizer: One copy of the CYP3A4*22 allele was detected. Therefore, this patient is expected to be an intermediate to extensive metabolizer. Reduced metabolism of drugs that are inactivated or activated by CYP3A4 is expected when compared to patients who are *1/*1. Coadministration of CYP3A4 inhibitors may increase the risk of toxicity for drugs inactivated by CYP3A4, or may cause lack of efficacy for drugs activated by CYP3A4. Intermediate metabolizer: Two copies of the CYP3A4*22 allele were detected. Therefore, this patient is expected to be an intermediate
metabolizer. Drugs that are inactivated or activated by CYP3A4 are metabolized at reduced rate when compared to patients who are *1/*1. Coadministration of CYP3A4 inhibitors may increase the risk of toxicity for drugs inactivated by CYP3A4, or may cause lack of efficacy for drugs activated by CYP3A4. Absence of the *22 allele does not rule out the possibility that a patient harbors another variant that can impact the function of this enzyme, drug response, or drug side effects. The CYP3A4 genotype is only one factor that should be taken into consideration for drug dosing. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Cytochrome P450 3A4 Genotype, Saliva**

**Clinical Information:** The cytochrome P450 (CYP) 3A4 enzyme is responsible for the metabolism of approximately 50% of drugs that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells, including lipid-lowering drugs. The CYP3A4 enzyme activity is highly variable. Interindividual differences in enzyme expression may be due to several factors including: variable homeostatic control mechanisms, disease states that alter homeostasis, up- or down-regulation by environmental stimuli, and genetic variation.(1) A CYP3A4 intron 6 variant, CYP3A4*22 (c.522-191C->T), affects hepatic expression of CYP3A4 and response to statin drugs. The CYP3A4*22 allele is associated with reduced CYP3A4 activity, which may result in a better response to lipid-lowering drugs, such as simvastatin, atorvastatin, or lovastatin. However, reduced CYP3A4 activity may also be associated with statin-induced myopathy, especially for simvastatin. Studies show that in livers with the wild-type genotype (homozygous C or CC) the CYP3A4 mRNA level and enzyme activity were 1.7- and 2.5-fold greater than in heterozygous CYP3A4*22 (CT) and homozygous CYP3A4*22 (TT) carriers, respectively. In 235 patients taking stable doses of drugs for lipid control, carriers of the T allele required significantly lower statin doses for optimal lipid control than did non-T carriers.(2) These results indicate that CYP3A4*22 markedly affects expression of CYP3A4 and could serve as a biomarker for CYP3A4 metabolizer phenotype. The reported allele frequency of CYP3A4*22 in Caucasians was 5% to 8%. The allele frequency is 4.3% in African Americans and in Chinese.

**Useful For:** Aids in determining therapeutic strategies for drugs that are metabolized by CYP3A4, including atorvastatin, simvastatin and lovastatin Genotyping patients who prefer not to have venipuncture done

**Interpretation:** Extensive metabolizer: The CYP3A4*22 allele was not detected. Therefore, this patient is expected to be an extensive metabolizer. Rapid metabolism of drugs that are inactivated or activated by CYP3A4 is expected. Coadministration of CYP3A4 inhibitors may increase the risk of toxicity for drugs inactivated by CYP3A4, or may cause lack of efficacy for drugs activated by CYP3A4. Intermediate to extensive metabolizer: One copy of the CYP3A4*22 allele was detected. Therefore, this patient is expected to be an intermediate to extensive metabolizer. Reduced metabolism of drugs that are inactivated or activated by CYP3A4 is expected when compared to patients who are *1/*1. Coadministration of CYP3A4 inhibitors may increase the risk of toxicity for drugs inactivated by CYP3A4, or may cause lack of efficacy for drugs activated by CYP3A4. Intermediate metabolizer: Two copies of the CYP3A4*22 allele were detected. Therefore, this patient is expected to be an intermediate
metabolizer. Drugs that are inactivated or activated by CYP3A4 are metabolized at reduced rate when compared to patients who are *1/*1. Coadministration of CYP3A4 inhibitors may increase the risk of toxicity for drugs inactivated by CYP3A4, or may cause lack of efficacy for drugs activated by CYP3A4. Absence of the *22 allele does not rule out the possibility that a patient harbors another variant that can impact the function of this enzyme, drug response, or drug side effects. The CYP3A4 genotype is only one factor that should be taken into consideration for drug dosing. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.


**FCYTP**

**Cytokine Panel**

**Interpretation:** Results are used to understand the pathophysiology of immune, infectious, or inflammatory disorders, or may be used for research purposes.

**Reference Values:**
- Tumor Necrosis Factor â€“ alpha
- Interleukin 2
- Interleukin 2 Receptor CD25 Soluble
- Interleukin 12
- Interferon gamma
- Interleukin 4
- Interleukin 5
- Interleukin 10
- Interleukin 13
- Interleukin 17
- Interleukin 1 beta
- Interleukin 6
- Interleukin 8

**CMVG**

**Cytomegalovirus (CMV) Antibodies, IgG, Serum**

**Clinical Information:** Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells.(1) Primary CMV infection in immunocompetent individuals may also manifest as a
mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation or from a newly acquired infection.(2,3) Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is 1 of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States the prevalence of CMV specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 to 11 and adults over 80 years old, respectively.(4)

Useful For: Determining whether a patient (especially transplant recipients, organ and blood donors) has had a recent infection or previous exposure to cytomegalovirus.

Interpretation: Positive cytomegalovirus (CMV) IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV, and are therefore considered susceptible to primary infection.

Reference Values:
Negative (reported as positive, negative, or equivocal)

Clinical References:

Cytomegalovirus (CMV) Antibodies, IgM and IgG, Serum

Clinical Information: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells.(1) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation or from a newly acquired infection.(2,3) Infection in these patient populations can affect almost any organ and lead to multi-organ failure. CMV is also responsible for congenital disease among newborns and is 1 of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States the prevalence of CMV specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 to 11 and adults over 80 years old, respectively.(4)

Useful For: Diagnosis of primary, acute phase infection with cytomegalovirus (CMV), especially in patients with infectious mononucleosis and pregnant women who, based on clinical signs or exposure, may have primary CMV infection. Determining whether a patient (especially transplant recipients, organ and blood donors) has had a recent infection or previous exposure to CMV.

Interpretation: IgM: A negative cytomegalovirus (CMV) IgM results suggest that the patient is not experiencing a recent infection. However, a negative result does not rule out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks post-infection. In cases of primary infection where the time of seroconversion is not well defined as high as 28% (10/36) of pregnant women did not demonstrate CMV IgM antibody. Positive CMV IgM
results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary rather than primary infections. IgG: Positive CMV IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV, and are therefore considered susceptible to primary infection. Equivocal CMV IgM or IgG results may occur during acute infection or may be due to non-specific binding reactions. Submit an additional sample for testing if clinically indicated.

Reference Values:
CMV IgM:
Negative (reported as positive, negative, or equivocal)

CMV IgG:
Negative (reported as positive, negative, or equivocal)

Clinical References:

Cytomegalovirus (CMV) Antibodies, IgM, Serum

Clinical Information: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells.(1) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation or from a newly acquired infection.(2,3) Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is 1 of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States the prevalence of CMV specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 to 11 and adults over 80 years old, respectively.(4)

Useful For: Diagnosis of primary, acute phase infection with cytomegalovirus (CMV), especially in patients with infectious mononucleosis and pregnant women who, based on clinical signs or exposure, may have primary CMV infection

Interpretation: A negative cytomegalovirus (CMV) IgM results suggest that the patient is not experiencing a recent infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection where the time of seroconversion is not well defined as high as 28% (10/36) of pregnant women did not demonstrate CMV-IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary, rather than primary, infections. Equivocal CMV IgM results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated.
Reference Values:
Negative (Reported as positive, negative, or equivocal)


Cytomegalovirus (CMV) CD8 T-Cell Immune Competence, Quantitative Assessment by Flow Cytometry

Clinical Information: Cytomegalovirus (CMV), a double-stranded DNA virus, belongs to the Herpesviridae family of viruses and is structurally similar to other herpes viruses. Although many human strains of CMV exist, there is little genetic homology between human CMV and CMV of other species. The reported seroprevalence rates of CMV range from 40% to 100% in the general population. In the urban United States, the seroprevalence of CMV has been reported to be 60% to 70%. However, data from Mayo Clinicâ€™s laboratory indicate that the seroprevalence in the Midwestern US population is closer to 30% (unpublished observations). Once CMV infection occurs, the virus spreads hematogenously to almost every organ. After acute infection, the virus enters a latent phase. Activation from this phase can be seen after acute illness, immunosuppression in allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation, or use of chemotherapy agents. CMV infection or reactivation has been implicated in allograft rejection in renal and cardiac transplantation. In cardiac transplants, CMV infection has been shown to contribute to accelerated development of transplant atherosclerosis (cardiac allograft vasculopathy). CMV remains a significant cause of morbidity and mortality after HSCT. Of allogeneic HSCT patients who are CMV-seropositive, 60% to 70% will experience reactivation and, without ganciclovir or other preemptive therapy, 20% to 30% will develop end-organ disease. CD8 T cells play a critical role in viral immunity, and CD8 T-cell effector functions include cytotoxicity and cytokine production. Cytotoxicity occurs after CD8 T-cell activation, causing target cell apoptosis. Cytotoxic T-cell responses mediate killing of target cells via 2 major pathways, granule-dependent (perforin and granzymes) and granule-independent (Fas and Fas ligand [FasL]) mechanisms. The granule-dependent pathway does not require the de novo synthesis of proteins by effector CD8 T cells, but rather it utilizes preformed lytic granules located within the cytoplasm. Among the proteins in these preformed lytic granules are the lysosomal-associated membrane proteins (LAMP), including LAMP-1 (CD107a) and LAMP-2 (CD107b). These proteins are not normally found on the surface of T cells. Degranulation of activated CD8 T cells occurs rapidly after T-cell receptor (TCR) stimulation, exposing CD107a and CD107b. The cytokines produced by activated T cells include interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), macrophage inflammatory protein 1 alpha (MIP-1 alpha), macrophage inflammatory protein 1 beta (MIP-1 beta), and interleukin-2 (IL-2). Several studies have shown the importance of cytotoxic T-cell responses to CMV in conferring protection from subsequent CMV disease. Antiviral drugs have helped reduce the incidence of early CMV infection, and acyclovir and ganciclovir have been the mainstay of antiviral treatment for a number of years, although these drugs have poor bioavailability. The development of the new antiviral drugs valacyclovir and valganciclovir (by the addition of a valine ester) has increased the bioavailability of these drugs by 10-fold. There is some data to suggest valganciclovir prophylaxis may be considered for HSCT patients who are at high risk for infection and disease, though there is a need for further study in this area. Two main strategies have been used for the prevention of early CMV infection and disease in CMV-seropositive patients and in seronegative recipients who receive a seropositive graft-preemptive therapy: -Patient monitoring for CMV infection and treatment only when CMV viremia is present. -Prophylactic management-where all patients receive treatment after transplantation with the goal of preventing CMV disease. The disadvantage of prophylactic therapy is that it requires monitoring for myelosuppression and infections-side effects of antiviral drug therapy. Despite this disadvantage, there are several reasons to consider prophylaxis, including the fact that the incidence of recurrent infections after treatment is 30% to 40%, patients receiving preemptive therapy have a 5% CMV disease.
break-through, and prophylaxis reduces the risk of viral reactivation. Late CMV infection occurs 3 months after transplantation and is now recognized as a significant cause of morbidity after allogeneic HSCT. These complications usually occur in the setting of continued immunosuppression for chronic graft-versus-host disease (GVHD). The clinical manifestations of late CMV disease differ slightly from those seen early after transplantation. Within the first 100 days after HSCT, almost all patients with CMV disease have CMV pneumonia and/or gastrointestinal disease. In late CMV disease, the more unusual manifestations of CMV infection (eg, CMV retinitis, CMV-associated bone marrow failure, or CMV encephalitis) tend to occur.(6) These late manifestations occur in a setting of continued CMV-specific T-cell immunodeficiency. Therefore, it is necessary to monitor CMV-specific CD8 T-cell responses, in addition to viral load, to effectively identify patients at higher risk of CMV disease. It has been shown that ganciclovir may delay the recovery of the protective CMV-specific T-cell response, which may contribute to the occurrence of late CMV disease.(7) The use of ganciclovir as early treatment after detection of CMV in blood or other body fluid and as a prophylaxis for CMV infection in bone marrow transplant (BMT) and heart transplant recipients has dramatically reduced the incidence of CMV in these immunocompromised hosts. Yet, early treatment and prophylaxis have not been uniformly successful, with up to 15% of BMT recipients developing CMV disease after discontinuation of antiviral therapy. Similarly, patients undergoing lung transplantation have been shown to be only transiently protected with antiviral agents. These data suggest that the CMV-specific responses necessary for protection may not recover during the time the host is receiving antiviral therapy. Ganciclovir exerts its antiviral effects at the stage of viral DNA replication and, therefore, in the presence of the drug, infected cells may express some of the immediate early and early gene products, but not the full complement of CMV genes required for replication and virion formation. In latently-infected CMV-seropositive individuals, the HLA class I-restricted cytotoxic T lymphocyte response to CMV is predominantly specific for epitopes derived from structural virion proteins. Therefore, in patients receiving ganciclovir, the viral antigens may be inadequate to activate host T-cell responses, resulting in the failure to reconstitute CMV-specific immunity. In fact, a prospective, randomized placebo-controlled study of ganciclovir prophylaxis revealed that when ganciclovir therapy is discontinued, a larger fraction of patients (who received the drug) are deficient in CMV-specific T-cell immunity at day 100 than in the placebo group.(7) That study also showed that bone marrow donor serology has an important influence on the early detection of virus-specific T-cell responses.(7) Not all medical centers use ganciclovir for prophylaxis; some use acyclovir and the same findings may apply in this case as well. In a more recent study, it was shown that impaired CD8 function was associated with the use of high-dose steroids, bone marrow as a source of stem cells, and CD8 T-cell lymphopenia.(3) In the absence of high-dose steroids, low-level subclinical CMV antigenemia was found to stimulate both CD4 and CD8 functional recovery in recipients of ganciclovir prophylaxis, suggesting that subclinical CMV reactivation while on antiviral therapy can be a potent stimulator of T-cell function.(3) Regardless of antiviral therapy, immunologic reconstitution remains the key element in protection from late-onset CMV disease. This test assesses the number of CMV-specific CD8 T cells and their function (activation via production of the cytokine IFN-gamma and cytotoxic potential via CD107a and CD107b as markers of degranulation) using a panel of 5 major histocompatibility complex (MHC) class I alleles (HLA A1, A2, B7, B8, and B35) along with their respective immunodominant CMV epitopes. This 3-part assay allows a comprehensive assessment of CMV-specific CD8 T cell immunity and, when combined with evaluation of viremia using molecular analyses, provides a more accurate picture of the nature of CMV reactivation and the corresponding immune response than evaluating viremia alone. Assessment of Global CD8 T-Cell Function: CD8 T cell activation occurs either through the TCR-peptide-MHC or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T cell activation (due to inherent cellular immunodeficiency or as a consequence over immunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. The incorporation of global CD8 T cell function in this assay is helpful in determining if the lack of CMV-specific (antigen-specific) response is due to a global impairment in CD8 T cell function, due to immunosuppression or other causes, or whether the lack of CMV CD8 T cell immunity is unrelated to overall CD8 T cell function. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+
B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Assessing cytomegalovirus (CMV)-specific immune competence in allo-hematopoietic stem cell transplantation patients who are at risk for developing late CMV disease (beyond day 100 after transplant) Assessing CMV-specific immune competence in solid organ transplant patients who are at high risk for CMV reactivation posttransplant Monitoring immune competence in patients post-primary CMV infection after transplant who are at risk for CMV reactivation after the cessation of antiviral prophylaxis Identifying individuals who are likely to be protected from posttransplant CMV infection and those who are at higher risk of CMV reactivation The global CD8 T cell immune competence assay is useful for determining over immunosuppression within the CD8 T cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** For allogeneic hematopoietic stem cell transplantation (HSCT) and solid organ transplant patients who are cytomegalovirus (CMV)-seropositive and at risk for CMV reactivation, posttransplant results should be compared to pretransplant (preconditioning/baseline) results. The report includes absolute CD3 and CD8 T-cell counts as well as a derived CMV-specific CD8 T-cell count (derived from CD3 and CD8 T-cell counts). The absolute count of CMV-CD8 T cells that are activated and have cytotoxic function in response to specific CMV peptide is also provided. The data from the 3 components of this assay should be interpreted together and not individually. In the setting of CMV viremia, frequent monitoring of CMV-immune competence helps define the evolution of the CMV immune response. In this clinical context, CMV-immune competence should be measured as frequently as viral load to determine correlation between the 2 parameters. CMV-specific CD8 T-cell counts may show a decline in numbers over time in the absence of active infection or antigenemia. The absence of CMV-specific CD8 T cells may be a risk factor in the immune-compromised or immune-incompetent transplant patient, who is at risk for CMV reactivation. The presence of CMV-specific CD8 T cells may not be protective in itself. If the CMV-specific CD8 T cells do not show appropriate cytotoxic function (due to the fact that they recognize CMV epitopes that do not effectively induce a cytotoxic response), these patients may be at higher risk of an inadequate immune response to CMV infection. While the reference values provide a guideline of CMV-specific CD8 T-cell numbers and function in a cohort of healthy individuals, baseline (pretransplant/preconditioning) assessments should be taken into consideration when determining CMV-specific immune competence posttransplant. Correlation between data from multiple posttransplant specimens (if available) and the presence or absence of viremia (or active CMV disease) also are useful in the interpretation of results. CD8 T cell counts are elevated when the immune system is initially reconstituted post-HSCT, and the CD4 to CD8 ratio can be inverted for about 12 months post-HSCT. Interferon-gamma (IFN-gamma) and CD107a/b expression below the defined reference range are consistent with a global impairment in CD8 T cell function, most likely due to over immunosuppression. IFN-gamma and CD107a/b levels greater than the defined reference range are unlikely to have any clinical significance.

**Reference Values:**

Total CD3 T cells: 884-5,830 x 10^3/mL
Total CD8 T cells: 168-1,847 x 10^3/mL
Total CMV CD8 T cells: 0-115 x 10^3/mL

The adult reference values were determined for healthy adult controls ages 20 to 80 years (n=94), for HLA A1, A2, B7, B8, and B35 alleles.

Reference values for CMV-specific T cells that are functional (interferon-gamma+, IFN-g+) and have cytotoxic activity (CD107a and CD107b expression, CD107a/b+):

Total CMV CD8 T-cells IFN-g: 0.028-52.200 x 10^3/mL
Total CMV CD8 T-cells CD107a/b: 0.252-50.760 x 10^3/mL
The 95% confidence interval reference values were determined from 102 healthy adult donors:
Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%
CD107a/b expression (as % CD8 T cells): 8.5-49.1%

The reference values were developed for each of the following 4 major histocompatibility complex class I alleles: A1, A2, B7, and B8 (n=45). We were unable to develop ranges for the B35 allele due to a lack of matching donors. The data is expressed as the absolute number of CMV-specific CD8 T cells that are IFN-gamma+ or CD107a/b+.

Clinical References:

**FCYTO**
**Cytomegalovirus (CMV) Genotypic Drug Resistance**
**Reference Values:**
Not Detected

**LCMV**
**Cytomegalovirus (CMV), Molecular Detection, PCR**
**Clinical Information:** Infection with cytomegalovirus (CMV) is a significant cause of morbidity and mortality in transplant recipients and other immunocompromised hosts. Specific neurologic syndromes associated with CMV infection include subacute radiculomyelopathy, peripheral neuropathy, and encephalitis. CMV-associated central nervous system (CNS) disease occurs most commonly in immunocompromised patients. Histologic evidence of CMV infections in autopsy brain tissue was identified in 20% to 40% of AIDS patients. In 2 separate studies, CMV (DNA) was the most common herpesvirus (29/181, 16/49) detected from cerebrospinal fluid of patients with AIDS. CNS infections with CMV can also occur in immunocompetent patients. CMV is a leading cause of congenital viral infections worldwide, and laboratory testing by real-time PCR is useful in the diagnosis of neonatal CMV disease.

**Useful For:** Rapid qualitative detection of cytomegalovirus DNA

**Interpretation:** Detection of cytomegalovirus (CMV) DNA in a specimen supports the clinical diagnosis of infection due to this virus. Studies indicate that CMV DNA is not detected by PCR in cerebrospinal fluid from patients without central nervous system disease caused by this virus.
Reference Values:
Negative

Clinical References:

Cytomegalovirus DNA Detection and Quantification, Plasma

Clinical Information: Cytomegalovirus (CMV) is a common and major cause of opportunistic infection in organ transplant recipients, causing significant morbidity and mortality. CMV infection and disease typically occur during the first year after organ transplantation after cessation of antiviral prophylaxis. Such infection usually manifests as fever, leukopenia, hepatitis, colitis, or retinitis. Other manifestations of CMV infection in this population may be more subtle and include allograft injury and loss, increased susceptibility to infections with other organisms, and decreased patient survival (ie, indirect effects). The risk of CMV disease is highest among organ recipients who are CMV seronegative prior to transplantation and receive allografts from CMV-seropositive donors (ie, CMV D+/R- mismatch). The infection is transmitted via latent CMV present in the transplanted organ donor and the virus subsequently reactivates, causing a primary CMV infection in the recipient. CMV disease may also occur from reactivation of the virus already present within the recipients. Factors, such as the type of organ transplanted, intensity of the antirejection immunosuppressive therapy, advanced age, and presence of comorbidities in the recipient, are also associated with increased risk for CMV disease after allograft transplantation. Lung, heart, small intestine, pancreas, and kidney-pancreas transplant recipients are at greater risk for CMV infection than kidney and liver transplant recipients. Among the various clinical laboratory diagnostic tests currently available to detect CMV infection, nucleic acid amplification tests (eg, PCR) are the most sensitive and specific detection methods. In addition, quantification of CMV DNA level in peripheral blood (ie, CMV viral load) is used routinely to determine when to initiate preemptive antiviral therapy, diagnose active CMV disease, and monitor response to antiviral therapy. A number of factors can affect CMV viral load results, including the specimen type (whole blood versus plasma), biologic properties of CMV, performance characteristics of the quantitative assay (eg, limit of detection, limits of quantification, linearity, and reproducibility), degree of immunosuppression, and intensity of antiviral therapy. In general, higher CMV viral loads are associated with tissue-invasive disease, while lower levels are associated with asymptomatic infection. However, the viral load in the peripheral blood compartment may be low or not detectable in some cases of tissue invasive disease. Since wide degree of overlap exists in CMV viral load and disease, rise in viral load over time is more important in predicting CMV disease than a single viral load result at a given time point. Therefore, serial monitoring (eg, weekly intervals) of organ transplant recipients with quantitative CMV PCR is recommended in such patients at risk for CMV disease. Since changes in viral load may be delayed by several days in response to antiviral therapy and immunosuppression, viral load should not be monitored more frequently than a weekly basis. Typically, CMV viral load changes of >0.5 log IU/mL are considered biologically significant changes in viral replication. Patients with suppression of CMV replication (ie, viral load of <137 or <2.1 log IU/mL at days 7, 14, and 21 of treatment) had shorter times to resolution of clinical disease than those without viral suppression. No degree of relative viral load reduction from pretreatment level was associated with faster resolution of CMV disease.

Useful For: Detection and quantification of cytomegalovirus (CMV) viremia Monitoring CMV disease
progression and response to antiviral therapy

**Interpretation:** The quantification range of this assay is 137 to 9,100,000 IU/mL (2.14 log to 6.96 log IU/mL), with a > or =95% limit of detection at 91 IU/mL (1.96 log IU/mL). A result of "Undetected" indicates the absence of cytomegalovirus (CMV) DNA in the plasma (see Cautions below). A result of "Detected, but <137 IU/mL (<2.14 log IU/mL)" indicates that CMV DNA is detected in the plasma, but the assay cannot accurately quantify the CMV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the level of CMV DNA (ie, viral load) present in the plasma. A result of "Detected, but >9,100,000 IU/mL (>6.96 log IU/mL)" indicates that CMV DNA level present in plasma is above 9,100,000 IU/mL (6.96 log IU/mL), and the assay cannot accurately quantify CMV DNA present above this level.

**Reference Values:**

Undetected

**Clinical References:**

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**ANCANCA**

9441

**Cytoplasmic Neutrophil Antibodies, Serum**

**Clinical Information:** Antineutrophil cytoplasmic antibodies (ANCA) can occur in patients with autoimmune vasculitis including Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), or organ-limited variants thereof such as pauci-immune necrotizing glomerulonephritis. (1) Detection of ANCA is a well-established diagnostic test for the evaluation of patients suspected of having autoimmune vasculitis. ANCA react with enzymes in the cytoplasmic granules of human neutrophils including proteinase 3 (PR3), myeloperoxidase (MPO), elastase, and cathepsin G. Antibodies to PR3 occur in patients with WG (both classical WG and WG with limited end-organ involvement) and produce a characteristic pattern of granular cytoplasmic fluorescence on ethanol-fixed neutrophils called the cANCA pattern. Antibodies to MPO occur predominately in patients with MPA and produce a pattern of perinuclear cytoplasmic fluorescence on ethanol-fixed neutrophils called the pANCA pattern.

**Useful For:** Antineutrophil cytoplasmic antibodies (cANCA and pANCA): - Evaluating patients suspected of having autoimmune vasculitis (both Wegener granulomatosis [WG] and microscopic polyangiitis) cANCA titer: - May be useful for monitoring treatment response in patients with WG (systemic or organ-limited disease); increasing titer suggests relapse of disease, while a decreasing titer suggests successful treatment. When used for diagnosis it is recommended that specific tests for proteinase 3 (PR3) ANCA and myeloperoxidase (MPO) ANCA be performed in addition to testing for cANCA and pANCA. (2) This panel of tests is available by ordering the VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum.

**Interpretation:** Positive results for antineutrophil cytoplasmic antibodies (cANCA or pANCA) are consistent with the diagnosis of Wegener granulomatosis (WG), either systemic WG with respiratory and renal involvement or limited WG with more restricted end-organ involvement. Positive results for pANCA are consistent with the diagnosis of autoimmune vasculitis including microscopic polyangiitis (MPA) or pauci-immune necrotizing glomerulonephritis. Sequential measurements of titers of cANCA may be useful to indicate the clinical course of patients with WG. Changes in titer of > or =2 serial dilutions are considered significant. (3) In patients with very low levels of cANCA, the immunofluorescent staining pattern may mimic the pANCA pattern. In patients with MPA, monitoring of disease activity may be performed by measuring MPO ANCA (MPO / Myeloperoxidase Antibodies, IgG, Serum).

**Reference Values:**

Negative
If positive for cANCA, results are titered.

D-Dimer, Plasma

Clinical Information: Thrombin, the terminal enzyme of the plasma procoagulant cascade, cleaves fibrinopeptides A and B from fibrinogen, generating fibrin monomer. Fibrin monomer contains D domains on each end of the molecule and a central E domain. Most of the fibrin monomers polymerize to form insoluble fibrin, or the fibrin clot, by repetitive end-to-end alignment of the D domains of 2 adjacent molecules in lateral contact with the E domain of a third molecule. The fibrin clot is subsequently stabilized by thrombin-activated factor XIII, which covalently cross-links fibrin monomers by transamidation, including dimerization of the D domains of adjacent fibrin monomers. The fibrin clot promotes activation of fibrinolysis by catalyzing the activation of plasminogen (by plasminogen activators) to form plasmin enzyme. Plasmin proteolytically degrades cross-linked fibrin, ultimately producing soluble fibrin degradation products of various sizes that include cross-linked fragments containing neoantigenic D-dimer (DD) epitopes. Plasmin also degrades fibrinogen to form fragments X, Y, D, and E. D-dimer immunoassays use monoclonal antibodies to DD neoantigen and mainly detect cross-linked fibrin degradation products, whereas the fibrinogen/fibrinolytic degradation products X, Y, D, and E and their polymers may be derived from fibrinogen or fibrin. Therefore, the blood content of D-dimer indirectly reflects the generation of thrombin and plasmin, roughly indicating the turnover or activation state of the coupled blood procoagulant and fibrinolytic mechanisms.

Useful For: Diagnosis of intravascular coagulation and fibrinolysis, also known as disseminated intravascular coagulation, especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time). Excluding the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability.

Interpretation: D-dimer values < or =250 ng/mL D-dimer units (DDU) (< or =0.50 mcg/mL fibrinogen equivalent units: FEU) are normal. Within the reportable normal range (110-250 ng/mL DDU; 0.22-0.50 mcg/mL FEU), measured values may reflect the activation state of the procoagulant and fibrinolytic systems, but the clinical utility of such quantitation is not established. A normal D-dimer result (< or =250 ng/mL DDU; < or =0.50 mcg/mL FEU) has a negative predictive value of approximately 95% for the exclusion of acute pulmonary embolism (PE) or deep vein thrombosis when there is low or moderate pretest PE probability. Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: Clinical or subclinical disseminated intravascular coagulation/intravascular coagulation and fibrinolysis -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism -Association with pregnancy, liver disease, inflammation, malignancy or hypercoagulable (procoagulant) states The degree of D-dimer increase does not definitively correlate with the clinical severity of associated disease states.

Reference Values:
< or =250 ng/mL D-Dimer Units (DDU)
< or =0.5 mcg/mL Fibrinogen Equivalent Units (FEU)

D-Lactate, Plasma

Clinical Information: D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts of D-lactate are present, individuals can experience metabolic acidosis, altered mental status (from drowsiness to coma), and a variety of other neurologic symptoms, particularly dysarthria and ataxia. D-lactic acidosis is typically observed in patients with a malabsorptive disorder, such as short-bowel syndrome, or, following a jejunoileal bypass. In addition, healthy children presenting with gastroenteritis may also develop the critical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, DLAC / D-Lactate, Plasma). However, as D-lactate is readily excreted in urine, DLAU / D-Lactate, Urine is the preferred specimen for D-lactate determinations.

Useful For: An adjunct to urine D-lactate (preferred), in the diagnosis of D-lactate acidosis

Interpretation: Increased levels are consistent with D-lactic acidosis. However, because D-lactate is readily excreted, urine determinations are preferred.

Reference Values:
0.0-0.25 mmol/L

Clinical References:

D-Lactate, Urine

Clinical Information: D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts are absorbed it can cause metabolic acidosis, altered mental status (from drowsiness to coma) and a variety of other neurologic symptoms, in particular dysarthria and ataxia. Although a temporal relationship has been described between elevations of plasma and urine D-lactate and the accompanying encephalopathy, the mechanism of neurologic manifestations has not been elucidated. D-lactic acidosis is typically observed in patients with short-bowel syndrome and following jejunoileal bypass resulting in carbohydrate malabsorption. In addition, healthy children presenting with gastroenteritis may also develop the critical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, DLAC / D-Lactate, Plasma). However, as D-lactate is readily excreted in urine, this is the preferred specimen for D-lactate determinations.

Useful For: Preferred test for diagnosing D-lactate acidosis, especially in patients with jejunoileal bypass and short-bowel syndrome

Interpretation: Increased levels are diagnostic.

Reference Values:
0.0-0.25 mmol/L

Clinical References:
Dairy and Grain Allergen Profile

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Dandelion, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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**FDANT 90363**

Dantrolene, Serum/Plasma

**Reference Values:**

- Reporting limit determined each analysis
- **Synonym(s):** Dantrium

- Usual therapeutic range: 0.2 - 3.5 mcg/mL

**DATE 82358**

Date, Fruit, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease...
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Deer Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Dehydroepiandrosterone (DHEA), Serum

Clinical Information: Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). The bulk of DHEA is secreted as a 3-sulfocoujugate dehydroepiandrosterone sulfate (DHEAS). Both hormones are albumin bound, but DHEAS binding is much tighter. As a result, circulating concentrations of DHEAS are much higher (>100-fold) compared to DHEA. In most clinical situations, DHEA and DHEAS results can be used interchangeably. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEAS back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA/DHEAS and their 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA/DHEAS levels fall by 80% or more and remain low until the onset of adrenarche at age 7 or 8 in girls and age 8 or 9 in boys. Adrenarche is a poorly understood phenomenon peculiar to higher primates, that is characterized by a gradual rise in adrenal androgen production. It precedes puberty, but is not casually linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt andro-genization. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults and some boys may develop early penile enlargement. Following adrenarche, DHEA/DHEAS levels increase until the age of 20 to a maximum roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA/DHEAS replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA/DHEAS to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA/DHEAS levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild-to-moderate elevations in DHEAS levels are idiopathic. However, pronounced elevations of DHEA/DHEAS may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid dehydrogenase deficiency is associated with excessive DHEA/DHEAS production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein (STAR) or 17 alpha-hydroxylase deficiency is characterized by low DHEA/DHEAS levels. See Steroid Pathways in Special Instructions.

Useful For: Diagnosing and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An initial screen in adults might include dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) and bioavailable testosterone measurement. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin and occasionally other androgenic steroids (eg, 17-hydroxyprogesterone). An adjunct in the diagnosis of congenital adrenal hyperplasia (CAH); DHEA/DHEAS measurements play a secondary role to the measurements of cortisol/cortisone, 17 alpha-hydroxyprogesterone, and androstenedione. Diagnosing and differential diagnosis of premature adrenarche

Interpretation: Elevated dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels >5-fold or more of the upper limit of normal can suggest the presence of an androgen-secreting adrenal tumor. DHEA/DHEAS levels are elevated in >90% of patients with such tumors. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce downstream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA/DHEAS. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA/DHEAS, often 5- to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA/DHEAS measurements. Consequently, DHEA/DHEAS testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering
a high DHEA/DHEAS level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA/DHEAS levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. See Steroid Pathways in Special Instructions.

**Reference Values:**
Premature: <4,000 ng/dL*  
0-1 day: <1,100 ng/dL*  
2-6 days: <870 ng/dL*  
7 days-1 month: <580 ng/dL*  
>1 month-23 months: <290 ng/dL*  
2-5 years: <230 ng/dL  
6-10 years: <340 ng/dL  
11-14 years: <500 ng/dL  
15-18 years: <660 ng/dL  
19-30 years: <1,300 ng/dL  
31-40 years: <1,000 ng/dL  
41-50 years: <800 ng/dL  
51-60 years: <600 ng/dL  
> or =61 years: <500 ng/dL


**Dehydroepiandrosterone (DHEA), Serum**

**Clinical Information:** Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotrophic hormone (ACTH). The bulk of DHEA is secreted as a 3-sulfoconjugate dehydroepiandrosterone sulfate (DHEAS). Both hormones are albumin bound, but DHEAS binding is much tighter. As a result, circulating concentrations of DHEAS are much higher (>100-fold) compared to DHEA. In most clinical situations, DHEA and DHEAS results can be used interchangeably. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEAS back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA/DHEAS and their 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA/DHEAS levels fall by 80% or more and remain low until the onset of adrenarche at age 7 or 8 in girls and age 8 or 9 in boys. Adrenarche is a poorly understood phenomenon, peculiar to higher primates, that is characterized by a gradual rise in adrenal androgen production. It precedes puberty, but is not casually linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults and some boys may develop early penile enlargement. Following adrenarche, DHEA/DHEAS levels increase until the age of 20 to a maximum roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA/DHEAS replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA/DHEAS to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA/DHEAS levels can cause symptoms or signs of...
hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild-to-moderate elevations in DHEAS levels are idiopathic. However, pronounced elevations of DHEA/DHEAS may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid dehydrogenase deficiency is associated with excessive DHEA/DHEAS production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein (STAR) or 17 alpha-hydroxylase deficiency is characterized by low DHEA/DHEAS levels. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnosing and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An initial screen in adults might include dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) and bioavailable testosterone measurement. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin and occasionally other androgenic steroids (eg, 17-hydroxyprogesterone). An adjunct in the diagnosis of congenital adrenal hyperplasia (CAH); DHEA/DHEAS measurements play a secondary role to the measurements of cortisol/cortisone, 17 alpha-hydroxyprogesterone, and androstenedione. Diagnosing and differential diagnosis of premature adrenarche.

**Interpretation:** Elevated dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels >5-fold or more of the upper limit of normal can suggest the presence of an androgen-secreting adrenal tumor. DHEA/DHEAS levels are elevated in >90% of patients with such tumors. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce downstream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA/DHEAS. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA/DHEAS, often 5-fold to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA/DHEAS measurements. Consequently, DHEA/DHEAS testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA/DHEAS level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA/DHEAS levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. See Steroid Pathways in Special Instructions.

**Reference Values:**
Premature: <40 ng/mL *
0-1 day: <11 ng/mL *
2-6 days: <8.7 ng/mL *
7 days-1 month: <5.8 ng/mL *
>1-23 months: <2.9 ng/mL *
2-5 years: <2.3 ng/mL
6-10 years: <3.4 ng/mL
11-14 years: <5.0 ng/mL
15-18 years: <6.6 ng/mL
19-30 years: <13 ng/mL
31-40 years: <10 ng/mL
41-50 years: <8.0 ng/mL
51-60 years: <6.0 ng/mL
> or =61 years: <5.0 ng/mL


Dehydroepiandrosterone Sulfate (DHEA-S), Serum

Clinical Information: Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone. The bulk of DHEA is secreted as a 3-sulfoconjugate (DHEA-S). Both hormones are albumin bound, but binding of DHEA-S is much tighter. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEA-S back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA-S and its 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA-S levels fall by 80% or more and remain low until the onset of adrenarche. Adrenarche is a poorly understood phenomenon peculiar to higher primates, which is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not causally linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization and is generally regarded as a benign condition, not needing intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Following adrenarche, DHEA-S levels increase until the age of 20 to a maximum level roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA-S replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA-S to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA-S levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild to moderate elevations in DHEA-S levels are idiopathic. However, pronounced elevations of DHEA-S may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid deficiency is associated with excessive DHEA-S production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidalogenic acute regulatory protein or 17 alpha-hydroxylase deficiencies are characterized by low DHEA-S levels. An initial workup in adults might also include total and bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) and, occasionally other androgenic steroids (eg, 17-hydroxyprogesterone).

Useful For: Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An adjunct in the diagnosis of congenital adrenal hyperplasia Diagnosis and differential diagnosis of premature adrenarche

Interpretation: Elevated dehydroepiandrosterone sulfate (DHEA-S) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels of 600 mcg/dL or more can suggest the presence of an androgen-secreting adrenal tumor. DHEA-S levels are elevated in more than 90% of patients with such tumors, usually well above 600 mcg/dL. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce down-stream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA-S. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA-S, often 5- to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA-S measurements. Consequently, DHEA-S testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA-S level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA-S levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. Girls below the age of 7 to 8 and boys before age 8 to 9, who present with early development of pubic hair, or, in boys, penile...
enlargement, may be suffering from either premature adrenarche or premature puberty, or both. Measurement of DHEA-S (DHES / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), dehydroepiandrosterone (DHEA_ / Dehydroepiandrosterone [DHEA], Serum), and androstenedione (ANST / Androstenedione, Serum), alongside determination of sensitive estradiol (EEST / Estradiol, Serum), testosterone and bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum), or free testosterone (TGRP / Testosterone, Total and Free, Serum), sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum), and luteinizing hormone (LH / Luteinizing Hormone [LH], Serum)/follicle-stimulating hormone (FSH / Follicle-Stimulating Hormone [FSH], Serum) levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the pre-puberty reference range. Levels of DHEA-S do not show significant diurnal variation. Many drugs and hormones can result in changes in DHEA-S levels. Whether any of these secondary changes in DHEA-S levels are of clinical significance and how they should be related to the established normal reference ranges is unknown. In most cases, the drug-induced changes are not large enough to cause diagnostic confusion, but when interpreting mild abnormalities in DHEA-S levels, drug and hormone interactions should be taken into account. Examples of drugs and hormones that can reduce DHEA-S levels include: insulin, oral contraceptive drugs, corticosteroids, central nervous system agents that induce hepatic enzymes (eg, carbamazepine, clomipramine, imipramine, phenytoin), many antilipemic drugs (eg, statins, cholestyramine), domapinergic drugs (eg, levodopa/dopamine, bromocryptine), fish oil, and vitamin E. Drugs that may increase DHEA-S levels include: metformin, troglitazone, prolactin, (and by indirect implication many neuroleptic drugs), danazol, calcium channel blockers (eg, diltiazem, amlodipine), and nicotine.

**Reference Values:**

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<thead>
<tr>
<th>Mean</th>
<th>Age</th>
<th>Reference Range (mcg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>&gt;14 days</td>
<td>16-96</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>22-184</td>
</tr>
<tr>
<td>Stage III</td>
<td>11.6 years</td>
<td>17-343</td>
</tr>
</tbody>
</table>

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-) 2 years. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) is usually reached by age 18. 18-29 years: 89-457 mcg/dL. 30-39 years: 65-334 mcg/dL. 40-49 years: 48-244 mcg/dL. 50-59 years: 35-179 mcg/dL. > or =60 years: 25-131 mcg/dL. FEMALES 1-14 days: DHEA-S levels in newborns are very elevated at birth but fall to prepubertal levels within a few days. Tanner Stages*
Stage V 14.5 years

44-332 mcg/dL

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-) 2 years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) is usually reached by age 18.

18-29 years: 44-332 mcg/dL
30-39 years: 31-228 mcg/dL
40-49 years: 18-244 mcg/dL
50-59 years: or =60 years:


Dementia, Autoimmune Evaluation, Serum

Clinical Information: The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders, with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms such as personality change, executive dysfunction, and psychiatric symptoms are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized within a triad of: 1) suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings, 2) the detection of cerebral spinal fluid (CSF) or serological biomarkers of autoimmunity and 3) a response to immunotherapy. Detection of neural autoantibodies in serum or CSF serves 2 purposes; to inform the physician of a likely autoimmune etiology and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, neuronal voltage-gated potassium channel (VGKC) antibodies were initially considered to be specific for autoimmune limbic encephalitis or disorders of peripheral nervous hyperexcitability, but over time other presentations have been reported, including a rapidly progressive course of cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1, ANNA-1; collapsin response-mediator protein-5 neuronal, CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor, NMDA-R), and thymoma (CRMP-5 IgG). Also, a
profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP 5 IgG, those findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful particularly when serum testing is negative. However, simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

**Useful For:** Investigating new onset dementia and cognitive impairment plus 1 or more of the following: - Rapid onset and progression - Fluctuating course - Psychiatric accompaniments (psychosis, hallucinations) - Movement disorder (myoclonus, tremor, dyskinesias) - Headache - Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) - Smoking history (20+ pack years) or other cancer risk factors - History of cancer - Inflammatory cerebral spinal fluid - Neuroimaging findings atypical for degenerative etiology

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: 1. Plasma membrane antibodies (N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor). These autoantibodies are all potential effectors of dysfunction. 2. Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). 3. Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**

- Antineuronal Nuclear Ab, Type 1 (ANNA-1) <1:240
- Antineuronal Nuclear Ab, Type 2 (ANNA-2) <1:240
- Antineuronal Nuclear Ab, Type 3 (ANNA-3) <1:240
- Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**

- Purkinje Cell Cytoplasmic Ab, Type 1 (PCA-1) <1:240
- Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2) <1:240
- Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr) <1:240
- Amphiphysin Antibody <1:240
- CRMP-5-IgG <1:240

**WESTERN BLOT**

- Paraneoplastic Western Blot Negative
- CRMP-5-IgG Western Blot Negative
- Amphiphysin Western Blot Negative

**ISLET CELL ANTIBODIES**
Glutamic Acid Decarboxylase (GAD65) Antibody
< or =0.02 nmol/L

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L

N-Methyl-D-aspartate receptor (NMDA-R) CBA
Negative
IFA: <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R) CBA
Negative
IFA: <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R) CBA
Negative
IFA: <1:120
NMO/AQP4-IgG
Negative


DEMEC 61507

Dementia, Autoimmune Evaluation, Spinal Fluid

Clinical Information: The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders, with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy-responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms such as personality change, executive dysfunction and psychiatric symptoms are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized within a triad of: 1) suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological
findings, 2) the detection of cerebral spinal fluid (CSF) or serological biomarkers of autoimmunity and 3) a response to immunotherapy. Detection of neural autoantibodies in serum or CSF serves 2 purposes; to inform the physician of a likely autoimmune etiology, and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, neuronal voltage-gated potassium channel (VGKC) antibodies were initially considered to be specific for autoimmune limbic encephalitis or disorders of peripheral nervous hyperexcitability, but over time other presentations have been reported, including rapidly progressive course of cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for one or two selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1, ANNA-1; collapsin response-mediator protein-5 neuronal, CRMP-5-IgG) ovarian teratoma (N-methyl-D-aspartate receptor, NMDA-R), and thymoma (CRMP-5 IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP 5 IgG, the findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful particularly when serum testing is negative. However, simultaneous testing on serum and CSF is recommended for some (such as NMDA-R antibody testing, since CSF is usually more informative).

Useful For: Investigating new onset dementia and cognitive impairment plus 1 or more of the following accompaniments: Rapid onset and progression Fluctuating course Psychiatric accompaniments (psychosis, hallucinations) Movement disorder (myoclonus, tremor, dyskinesias) Headache Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus). Smoking history (20+ pack years) or other cancer risk factors. History of cancer Inflammatory cerebral spinal fluid Neuroimaging findings atypical for degenerative etiology

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient’s immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia. 1. Plasma membrane antibodies (N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-aminobutyric acid (GABA-B) receptor). These autoantibodies are all potential effectors of dysfunction. 2. Neuronal nuclear autoantibody type 1 (ANNA-1) or type 3 (ANNA-3). 3. Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

Reference Values:
Anti-neuronal Nuclear Ab, Type 1 (ANNA-1), CSF: <1:2
Anti-neuronal Nuclear Ab, Type 2 (ANNA-2), CSF: <1:2
Anti-neuronal Nuclear Ab, Type 3 (ANNA-3), CSF: <1:2
Purkinje Cell Cytoplasmic Ab, Type1 (PCA-1), CSF: <1:2
Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2), CSF: <1:2
Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr), CSF: <1:2
Amphiphysin Ab, CSF: <1:2
CRMP-5-IgG Ab, CSF: <1:2
Paraneoplastic Western Blot, CSF: Negative
CRMP-5-IgG Western Blot, CSF: Negative
Amphiphysin Western Blot, CSF: Negative
Glutamic Acid Decarboxylase-65 (GAD65), CSF: < or =0.02 nmol/L
Neuronal Voltage-Gated Potassium Channel-Complex Autoantibody, Spinal Fluid: < or =0.02 nmol/L
N-Methyl-D-aspartate receptor (NMDA-R), CSF
CBA: Negative
IFA: <1:2
2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid receptor (AMPA-R), CSF
CBA: Negative
IFA: <1:2
Gamma-Amino Butyric acid-type B receptor (GABA-B-R), CSF
CBA: Negative
IFA: <1:2
Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1), CSF: <1:2
NMO/AQP4-IgG, CSF: Negative


Dementia, Autoimmune Interpretation, Serum
Reference Values:
Only orderable as part of a profile. For more information see DEMES / Dementia, Autoimmune Evaluation, Serum.

Dementia, Autoimmune Interpretation, Spinal Fluid
Reference Values:
Only orderable as part of a profile. For more information see DEMEC / Dementia, Autoimmune Evaluation, Spinal Fluid.

Dengue Virus Antibody, IgG and IgM, Serum
Clinical Information: Dengue virus (DV) is a globally distributed Flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescent signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM/IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure and, therefore, testing of acute and convalescent sera may be necessary to make the diagnosis. As an adjunct to serologic testing, identification of early DV infection may be made by detection of the DV NS1 antigen. NS1 antigenemia is detectable within 24 hours of infection and up to 9 days following symptom onset. The DV NS1 antigen can be detected using DNS1 / Dengue Virus NS1 Antigen, Serum by enzyme immunoassay.
Useful For: An aid in the diagnosis of dengue virus infection
Interpretation: IgG: The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. IgM: The presence of IgM-class antibodies to
DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens drawn too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, drawn approximately 10 to 12 days following exposure should be tested.

Reference Values:
IgG: Negative
IgM: Negative

Reference values apply to all ages.


**Dengue Virus Antibody/Antigen Panel, Serum**

**Clinical Information:** Dengue virus (DV) is a globally distributed Flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM/IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure and therefore testing of acute and convalescent sera may be necessary to make the diagnosis. As an adjunct to serologic testing, identification of early DV infection may be made by detection of the DV NS1 antigen. NS1 antigenemia is detectable within 24 hours of infection and up to 9 days following symptom onset. The DV NS1 antigen can be detected using DNSAG / Dengue Virus NS1 Antigen, Serum by enzyme immunoassay. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic and molecular based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV provides optimal diagnostic potential for both early and late dengue disease.

**Useful For:** An aid in the diagnosis of dengue virus infection

**Interpretation:** IgG: The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. IgM: The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens drawn too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, drawn approximately 10 to 12 days following exposure should be tested. Nonstructural protein 1 (NS1): The presence of dengue NS1 antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). The absence of dengue
NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative if samples collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

**Reference Values:**
- IgG: Negative
- IgM: Negative
- NS1: Negative

Reference values apply to all ages.

**Clinical References:**

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**DNSAG 36781**

**Dengue Virus NS1 Antigen, Serum**

**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic and molecular based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV (DENGMM) provides optimal diagnostic potential for both early and late dengue disease.

**Useful For:** An aid in the diagnosis of dengue virus infection

**Interpretation:** Positive: The presence of dengue nonstructural protein 1 (NS1) antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). Negative: The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative if specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

**Reference Values:**
- Negative

Reference values apply to all ages.

**Clinical References:**
**Dentatorubral-Pallidoluysian Atrophy (DRPLA) Gene Analysis**

**Clinical Information:** Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder characterized by ataxia, choreoathetosis, dementia, and psychiatric disturbance in adults and ataxia, myoclonus, seizures, and progressive intellectual deterioration in children. Characteristic neuropathologic observations include degeneration of the dentatorubral and pallidoluysian systems of the central nervous system. The prevalence of DRPLA depends on the geographic and ethnic origin of the population being studied. DRPLA was first described in a European individual without a family history; however, it is predominantly found as an inherited condition and is most prevalent in Japan (0.2-0.7 per 100,000). Although rare, DRPLA has been identified in other populations including Europe and North America. DRPLA is caused by an expansion of the CAG trinucleotide repeat in the ATN1 (DRPLA) gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 7 to 35. In affected individuals the CAG expansion ranges from 48 to 93 repeats. As with other trinucleotide repeat disorders, anticipation is frequently observed, and larger CAG expansions are associated with earlier onset and a more severe and rapid clinical course. In DRPLA, the observed anticipation appears to be significantly greater in paternal transmissions.

**Useful For:** Molecular confirmation of a diagnosis of dentatorubral-pallidoluysian atrophy (DRPLA) for symptomatic patients Predictive testing for individuals with a family history of DRPLA and a documented expansion in the ATN1 gene in an affected family member

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles: 7-35 CAG repeats
Abnormal alleles: 49-93 CAG repeats
An interpretive report will be provided.

**Clinical References:**

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**Deoxycorticosterone (DOC), Serum**

**Reference Ranges:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 28w) Day 4</td>
<td>20 - 105</td>
</tr>
<tr>
<td>Premature (34 - 36w) Day 4</td>
<td>28 - 78</td>
</tr>
<tr>
<td>Newborn</td>
<td>Levels are markedly elevated at birth and decrease rapidly during the first week to the range of 7 - 49 as found in older infants.</td>
</tr>
<tr>
<td>1 - 11m</td>
<td>7 - 49</td>
</tr>
<tr>
<td>Prepubertal Children</td>
<td>2 - 34</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>2 - 19</td>
</tr>
</tbody>
</table>

**Test Performed By:** Esoterix Endocrinology
4301 Lost Hills Road
Calabasas Hills, CA 91301
Deoxypyridinoline Crosslinks, Urine

Reference Values:
Deoxypyridinoline Urine-ratio to CRT  
Adult Male: 2.3 – 8.7 nmol/mmol  
Premenopasual Adult Female: 3.1 – 8.7 nmol/mmol

Creatinine, Urine â€“ per volume  
No reference interval

The target value for treated post-menopausal adult females is the same as the Premenopausal reference interval.

Dermatophagoides microceras, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical Information:** Dermatopathology involves histologic examination of skin biopsy and oral mucosal specimens.

**Useful For:** Histologic diagnosis and differential diagnosis of cutaneous diseases

**Interpretation:** Histologic diagnosis is based primarily on interpretation of hematoxylin and eosin-stained sections. Special histochemical stains, such as alcian blue, Giemsa, or periodic acid-Schiff may be necessary in some cases. Interpretation is based on evaluation of patterns including architectural and cytologic details, which are included in a microscopic description.

**Reference Values:**
Diagnosis and description of microscopic findings


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**Des-Gamma-Carboxy Prothrombin (DCP), Serum**

**Clinical Information:** Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many hepatocellular carcinoma (HCC) cells, and an abnormal prothrombin with all or some of unconverted glutamic acid is secreted. Therefore, this noncarboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to alpha fetoprotein (AFP) and third electrophoretic form of lentil lectin-reactive AFP% (AFP-L3%) for assessing the risk of developing HCC. The elevation of both AFP-L3 and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3%, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3%, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion and/or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC.

**Useful For:** Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma (HCC) An aid in the monitoring of HCC patients post therapy if des-gamma-carboxy prothrombin (DCP) level was elevated prior to therapy. An elevated DCP level is associated with increased risk of recurring HCC.

**Interpretation:** In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing hepatocellular carcinoma (HCC) is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%).

**Reference Values:**
<7.5 ng/mL

Desipramine, Serum

Clinical Information: Desipramine is a tricyclic antidepressant; it also is a metabolite of imipramine. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects: dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations in excess of 300 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 300 ng/mL.

Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

Interpretation: Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with levels > or =300 ng/mL.

Reference Values:
Therapeutic concentration: 100-300 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


Desmoglein 1 (DSG1) and Desmoglein 3 (DSG3), IgG Antibodies, Serum

Clinical Information: Pemphigus includes a group of often fatal autoimmune, blistering diseases characterized by intraepithelial lesions. Pemphigus vulgaris and its variants may present with oral or mucosal lesions alone or with mucosal plus skin lesions. Pemphigus foliaceus and variants present with skin lesions alone. Indirect immunofluorescence (IIF) studies reveal that both forms of pemphigus are caused by autoantibodies to cell surface antigens of stratified epithelia or mucous membranes and skin. These antibodies bind to calcium-dependent adhesion molecules in cell surface desmosomes, notably desmoglein 1 (DSG1) in pemphigus foliaceus and desmoglein 3 (DSG3) and/or DSG1 in pemphigus vulgaris. Desmogleins are protein substances located in and on the surface of keratinocytes. These proteins have been shown to be a critical factor in cell-to-cell adhesion. Antibodies to desmogleins can result in loss of cell adhesion, the primary cause of blister formation in pemphigus. The diagnosis of pemphigus depends on biopsy and serum studies that characterize lesions and detect the autoantibodies that cause them. Originally, the serum studies were performed by IIF using monkey esophagus and other tissue substrates. The identification of the reactive antigens as DSG1 and DSG3 has made it possible to
develop highly specific and sensitive enzyme-linked immunosorbent assay methods.

**Useful For:** Preferred screening test for patients suspected to have an autoimmune blistering disorder of the skin or mucous membranes (pemphigus) As an aid in the diagnosis of pemphigus Monitoring treatment response in patients with a confirmed diagnosis of pemphigus

**Interpretation:** Antibodies to desmoglein 1 (DSG1) and desmoglein 3 (DSG3) have been shown to be present in patients with pemphigus. Many patients with pemphigus foliaceus, a superficial form of pemphigus have antibodies to DSG1. Patients with pemphigus vulgaris, a deeper form of pemphigus, have antibodies to DSG3 and sometimes DSG1 as well. Antibody titer correlates in a semiquantitative manner with disease activity in many patients. Patients with severe disease can usually be expected to have high titers of antibodies to DSG. Titers are expected to decrease with clinical improvement. Our experience demonstrates a very good correlation between DSG1 and DSG3 results and the presence of pemphigus. Adequate sensitivities and specificity for disease are documented. However, in those patients strongly suspected to have pemphigus either by clinical findings or by routine biopsy, and in whom the DSG assay is negative, the IIF test (CIFS / Cutaneous Immunofluorescence Antibodies [IgG], Serum) is recommended. For further information, see Cutaneous Immunofluorescence Testing in Special Instructions.

**Reference Values:**

DESMOGLEIN 1
- <14.0 U (negative)
- 14.0-20.0 U (indeterminate)
- >20.0 U (positive)

DESMogleIN 3
- <9.0 U (negative)
- 9.0-20.0 U (indeterminate)
- >20.0 U (positive)

**Clinical References:**

**DSRCT 35330**

**Desmoplastic Small Round-Cell Tumor by Reverse Transcriptase PCR (RT-PCR)**

**Clinical Information:** Desmoplastic small round-cell tumor (DSRCT) is a member of the small round-cell tumor group that also includes rhabdomyosarcoma, synovial sarcoma, lymphoma, Wilms tumor, and Ewing sarcoma. DSRCT is a type of sarcoma that affects mainly children and adolescent males, usually in the form of widespread intra-abdominal growth not related to any specific organ system. The tumor is composed of angulated nests of small round cells with an abundant desmoplastic stroma. The tumor cells show multiphenotypic differentiation and are usually positive for cytokeratin and desmin.(1-4) These tumors can express renal, epithelial, muscle, and endocrine markers. While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small round-cell tumor group can be very difficult by light microscopic examination alone, especially true when only small-needle biopsy specimens are available for examination. The use of histochemical and immunohistochemical stains (eg, desmin, cytokeratin, and WT1) can assist in establishing the correct diagnosis, they cannot distinguish between DSRCT and other small round-cell tumors. Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas and are useful in the diagnosis of these lesions.(1-4) DSRCT is associated with a unique chromosomal translocation t(11;22)(p13;q12) that involves the EWSR1 and the WT1 genes. EWSR1 is the breakpoint site of translocations associated with Ewing sarcoma and WT1
is a gene altered in some Wilms tumors. The translocation results in a fusion of the 2 genes with expression of a chimeric EWSR1-WT1 product. The most common breakpoints involve the intron between EWSR1 exon 7 and 8 and the intron between WT1 exons 7 and 8. Analyses of these transcripts have shown an in-frame fusion of RNA encoding the amino-terminal domain of EWSR1 to the zinc finger of the DNA-binding domain of WT1.

**Useful For:** Supporting the diagnosis of desmoplastic small round-cell tumor

**Interpretation:** A positive EWSR1-WT1 result is consistent with a diagnosis of desmoplastic small round-cell tumor (DSRCT). Sarcomas other than DSRCT, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of DSRCT.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

FDXM
**Dexamethasone**

<table>
<thead>
<tr>
<th>Reference Values:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Units = ng/dL</strong></td>
</tr>
<tr>
<td>Adults baseline: &lt;30</td>
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<tr>
<td>8:00 AM following 1 mg dexamethasone previous evening: 140 - 295</td>
</tr>
<tr>
<td>8:00 AM following 8 mg dexamethasone (4 x 2 mg doses) previous day: 1600 - 2850</td>
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FDXAP
**Dexedrine (Dextroamphetamine)**

<table>
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<tbody>
<tr>
<td><strong>Reference Range:</strong> 10 – 100 ng/mL</td>
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FDM
**Dextromethorphan (DM), Serum**

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<tr>
<td><strong>Reference Range:</strong> 2.0 - 6.0 ng/mL</td>
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</table>

DME
**Diabetes Mellitus Type 1 Evaluation**

<table>
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<tr>
<th>Clinical Information:</th>
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<tbody>
<tr>
<td>Islet cell autoantibodies were first recognized to be associated with type 1 diabetes mellitus in 1974. Several islet cell-specific autoantigens have been identified in recent years. These include glutamic acid decarboxylase 65 (GAD65), the tyrosine phosphatase-related islet antigen 2 (IA-2), and insulin. The sensitivities of these autoantibodies for type 1 diabetes in an international collaborative study were 91% (GAD65 antibody), 74% (IA-2 antibody), and 49% (insulin antibody) when tested in isolation. When tested in combination, the combined sensitivity for type 1 diabetes was up to 98%, with a specificity of 98% to 100%. These autoantibodies also are detectable before the clinical diagnosis of type 1 diabetes.</td>
</tr>
</tbody>
</table>
onset of diabetes. Prospective studies in relatives of patients with type 1 diabetes have shown that the detection of 1 or more islet autoantibodies is an early marker of progression to type 1 diabetes. Among first-degree relatives of those with type 1 diabetes, the cumulative risk of developing diabetes at 5 years after testing was 17% if seropositive for 1 antibody, 39% if seropositive for 2 antibodies, and 70% if seropositive for 3 antibodies. (3) Autoantibody profiles identifying patients destined to develop type 1 diabetes are usually detectable in serum before age 3. Some patients with type 1 diabetes are initially misdiagnosed as having type 2 diabetes because of symptom onset in adulthood, societal obesity, and initial insulin-independence. Detection of 1 or more islet autoantibodies allows identification of patients with "latent autoimmune diabetes in adulthood" amongst those with presumed type 2 diabetes.

**Useful For:** Distinguishing type 1 from type 2 diabetes mellitus Identifying individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes) Predicting future insulin requirement treatment in patients with adult-onset diabetes

**Interpretation:** Seropositivity for 1 or more islet cell autoantibodies is supportive of: - A diagnosis of type 1 diabetes. Only 2% to 4% of patients with type 1 diabetes are antibody negative; 90% have more than 1 antibody marker, and 70% have 3 markers. (1) Patients with gestational diabetes who are antibody seropositive are at high risk for diabetes postpartum. Rarely, diabetic children test seronegative, which may indicate a diagnosis of maturity-onset diabetes of the young in clinically suspicious cases. - A high risk for future development of diabetes. Among 44 first degree relatives of patients with type 1 diabetes, those with 3 antibodies had a 70% risk of developing type 1 diabetes within 5 years. (3) - A current or future need for insulin therapy in patients with diabetes. In the UK Prospective Diabetes Study, 84% of those classified clinically as having type 2 diabetes and seropositive for glutamic acid decarboxylase 65 required insulin within 6 years, compared to 14% that were antibody negative. (4)

**Reference Values:**

**GLUTAMIC ACID DECARBOXYLASE (GAD65) ANTIBODY**

< or =0.02 nmol/L

Reference values apply to all ages.

**INSULIN ANTIBODIES**

< or =0.02 nmol/L

Reference values apply to all ages.

**ISLET ANTIGEN 2 (IA-2) ANTIBODY**

< or =0.02 nmol/L

Reference values apply to all ages.

**Clinical References:**


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**Diazepam and Nordiazepam, Serum**

**Clinical Information:** Diazepam, a benzodiazepine derivative, is an anxiolytic agent that reduces neuronal depolarization resulting in decreased action potentials. It enhances the action of gamma-aminobutyric acid (GABA) by tightly binding to A-type GABA receptors, thus opening the membrane channels and allowing the entry of chloride ions. It is also used as a muscle relaxant, procedural sedation agent, and sedative-hypnotic agent to treat withdrawal states (ie, ethanol), along with other conditions (seizures). Diazepam is metabolized to several metabolites in the liver including temazepam, oxazepam, and nordiazepam (desmethyldiazepam) and the clearance of the drug is reduced considerably in the elderly and in patients with hepatic disease. Therapeutic assessment typically includes measurement of both the
parent drug (diazepam) and the active metabolite (nordiazepam).

**Useful For:** Assessing compliance Monitoring for appropriate therapeutic level Assessing toxicity

**Interpretation:** For seizures: Serum concentrations are not usually monitored during early therapy because response to the drug can be monitored clinically as seizure control. If seizures resume despite adequate therapy, another anticonvulsant must be considered. Toxicity is commonly seen when diazepam plus nordiazepam concentrations exceed 3,000 ng/mL. Adverse effects of benzodiazepines in therapeutic doses usually reflect the drug's pharmacology and include sedation, slurred speech, and ataxia. Respiratory depression/arrest may occur with large overdoses or following rapid IV injection with short-acting benzodiazepines.

**Reference Values:**
Therapeutic concentrations
Diazepam and Nordiazepam: 200-2,500 ng/mL

**Clinical References:**
2. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, Edited by CA Burtis, ER Ashwood, DE Bruns, WB Saunders Company, Philadelphia, PA, 2011, Table 60.2, pp 1109-1188

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**Digitoxin, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Digitoxin
Therapeutic Range: 10 - 30 ng/mL

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**Digoxin, Free, Serum**

**Clinical Information:** Digoxin, a widely prescribed cardiac drug, has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue concentrations). While excess digoxin can have serious side effects (eg, cardiac dysrhythmias, heart failure, seizures, death), it is one of the few therapeutic drugs for which antidotal therapy is available. In toxic situations, antibody fragment therapy, which involves the administration of antibodies to digoxin (eg, Digibind, Digoxin Immune Fab), is indicated. In manufacturing of Digibind, papain cleaves digoxin-specific IgG antibody into 2 antigen binding-site fragments (Fab fragments). These fragments bind to digoxin, block the active site of the digoxin molecule, and make it unavailable to its receptor molecule and biologically inactive. The Fab fragment-digoxin complex is then excreted by the kidney. Total digoxin concentration in blood increases approximately 10 to 30 fold after administration of Fab fragments. On the other hand, the unbound (free) fraction, which is responsible for its pharmacological activity, decreases. Traditional digoxin assays performed by immunoassay (eg, DIG / Digoxin, Serum) measure both Fab fragment-bound (inactive) digoxin and free (active) digoxin (ie, total digoxin), and are unsuitable for managing patients when digoxin-specific Fab fragment therapy has been administered. Assays that only measure free digoxin levels are necessary in such situations. The kidneys provide the main route of Fab fragment elimination from the body. In patients with normal renal function, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of 15 to 20 hours. Ordinarily, improvement signs or symptoms of digoxin intoxication begins within a half hour or less after initiation of Fab fragment therapy. Clearance may be delayed in patients with renal failure. In such patients, toxicity may recur if previously bound drug is released from the Fab fragments, resulting in increased levels of free digoxin. Digoxin-like immunoreactive factors (DLIFs) are endogenous substances that can cross-react with testing antibodies used in some digoxin immunoassays, causing erroneous results. DLIFs may be seen in certain volume-expanded patients such as neonates, patients with renal or liver disease, and in women in the third trimester of pregnancy being treated with digoxin. DLIFs are strongly bound to proteins and, in this assay, are removed prior to testing. The following ordering guidelines are offered: -When creatinine
clearance is <30 mL/min/surface area: order free digoxin levels daily for 12 days (or until dismissal)
-When creatinine clearance is > or =30 mL/min/surface area (and patient is not on renal-replacement
therapy): order free levels daily for 72 hours, as long as last level is not supratherapeutic (these patients
are expected to have good clearance and a lower risk for reintoxication) - Also order total digoxin levels
every other day during the time periods above, with a goal of determining whether there is correlation
between changes in free and total levels.

**Useful For:** Evaluating recrudescent (breakthrough) digoxin toxicity in renal-failure patients Assessing
the need for more antidigoxin Fab to be administered Deciding when to reintroduce digoxin therapy
Monitoring patients with possible digoxin-like immunoreactive factors (DLIFs)

**Interpretation:** The target therapeutic is 0.4 to 1.5 ng/mL. Toxicity may be seen when free digoxin
concentrations are > or =3.0 ng/mL. Pediatric patients may tolerate higher concentrations. Therapeutic
concentrations for free digoxin are 25% lower than therapeutic values for total digoxin due to the
separation of protein-bound digoxin in the assay.

**Reference Values:**
Therapeutic concentration: 0.4-1.5 ng/mL
Toxic concentration: > or =3.0 ng/mL
Pediatric toxic concentrations may be higher.

**Clinical References:**
measurements by immunoassays in presence of antidote (Digibind). Clin Chim Acta 1999;283:159-169
2. Package insert: DIGIBIND Digoxin Immune FAB (Ovine). GlaxoSmithKline, Research Triangle Park
Comparison four digoxin immunoassays with respect to interference from digoxin-like immunoreactive
overview. Arch Pathol Lab Med 1999;123:822-823

### Digoxin, Serum

**Clinical Information:** Compounds in the digitalis family of glycosides consist of a steroid nucleus, a
lactone ring, and a sugar. Digoxin is widely prescribed for the treatment of congestive heart failure and
various disturbances of cardiac rhythm. Digoxin improves the strength of myocardial contraction and
results in the beneficial effects of increased cardiac output, decreased heart size, decreased venous
pressure, and decreased blood volume. Digoxin therapy also results in stabilized and slowed ventricular
pulse rate. These therapeutic effects are produced through a network of direct and indirect interactions
upon the myocardium, blood vessels, and the autonomic nervous system. Digoxin is well absorbed after
oral administration and is widely distributed to tissues, especially the heart, kidney, and liver. A number
of factors can alter normal absorption, distribution, and bioavailability of the drug, including naturally
occurring enteric bacteria in the bowel, presence of food in the gut, strenuous physical activity, ingestion
of quinine or quinidine, and concomitant use of a wide range of drugs. Children generally require higher
concentrations of digoxin. After oral administration, there is an early rise in serum concentration.
Equilibration of serum and tissue levels occurs at approximately 6 to 8 hours. For this reason, blood
specimens for digoxin analysis should be drawn at least 6 to 8 hours after drug administration. Digoxin is
excreted primarily in the urine. The average elimination half-life is 36 to 40 hours, but may be
considerably prolonged in those with renal disease, causing digoxin accumulation and toxicity. Symptoms
of digoxin toxicity often mimic the cardiac arrhythmia's for which the drug was originally prescribed (eg,
heart block and heart failure). Other typical symptoms of toxicity include gastrointestinal effects,
including anorexia, nausea, vomiting, abdominal pain and diarrhea, and neuropsychologic symptoms,
such as fatigue, malaise, dizziness, clouded or blurred vision, visual and auditory hallucination, paranoid
ideation, and depression. Toxicity of digoxin may reflect several factors: the drug has a narrow
therapeutic window (a very small difference exists between therapeutic and toxic tissue levels);
individuals vary in their ability to metabolize and respond to digoxin; absorption of various oral forms
of digoxin may vary over a 2-fold range; susceptibility to digitalis toxicity apparently increases with age.
Useful For: Monitoring digoxin therapy

Interpretation: The therapeutic range is 0.5 to 2.0 ng/mL. Levels >4.0 ng/mL may be potentially life-threatening.

Reference Values:
Therapeutic concentration: 0.5-2.0 ng/mL
Toxic concentration: > or =4.0 ng/mL
Pediatric toxic concentrations may be higher.
Reference values have not been established for patients that are <16 years of age.


**Dihydrorhodamine (DHR) Flow Cytometric N-Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Test, Blood**

Clinical Information: This assay can be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory mutations in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function.(1) Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with phorbol myristate acetate (PMA), indicating normal NADPH oxidase activity, but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, indicates a signaling defect in Rac2 deficiency.(2)

Useful For: Diagnosis of Rac2 deficiency

Interpretation: An interpretive report will be provided, in addition to the quantitative values described in Clinical Information. Interpretation of the results of the quantitative dihydorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after N-formyl-methionyl-leucyl-phenylalanine stimulation, and the mean fluorescence intensity.

Reference Values:

<table>
<thead>
<tr>
<th>Result Name</th>
<th>Unit</th>
<th>Cutoff for defining normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% fMLP ox-DHR+</td>
<td>%</td>
<td>&gt; or =10%</td>
</tr>
<tr>
<td>MFI fMLP ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =2</td>
</tr>
<tr>
<td>Control % fMLP ox-DHR+</td>
<td>%</td>
<td>&gt; or =10%</td>
</tr>
<tr>
<td>Control MFI fMLP ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =2 The appropriate age-related reference values for Absolute Neutrophil Count will be provided on the report.</td>
</tr>
</tbody>
</table>

Acetate (PMA) Test, Blood

Clinical Information: Chronic granulomatous disease (CGD) is caused by genetic defects in the gene components that encode the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. These defects result in an inability to produce superoxide anions required for killing of bacterial and fungal organisms. Other clinical features include a predisposition to systemic granulomatous complications and autoimmunity. There are 5 known genetic defects associated with the clinical phenotype of CGD. The gene defects include mutations in the CYBB gene, encoding the gp91phox protein, which is X-linked and accounts for approximately 70% of CGD cases. Other gene defects are autosomal recessive: NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), and NCF4 (p40phox). Typically, patients with X-linked CGD have the most severe disease, while patients with p47phox defects tend to have the best outcomes. Mutations in NCF4 encoding the p40phox protein have been the most recently described and appears to be associated with more gastrointestinal disease with fewer infections. There is significant clinical variability even among individuals with similar mutations, in terms of NADPH oxidase function, indicating that there can be several modulating factors including the genetic defect, infection history, and granulomatous and autoimmune complications. There appears to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can be treated with hematopoietic cell transplantation (HCT), which can be effective for the inflammatory and autoimmune manifestations. It has been shown that survival of patients with CGD was strongly associated with residual reactive oxygen intermediate (ROI) production, independent of the specific gene defect. Measurement of NADPH oxidase activity through the dihydrorhodamine (DHR) flow cytometry assay contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD includes evaluation of NADPH oxidase function in neutrophils, using either the nitroblue tetrazolium test (NBT) or the more analytically sensitive DHR test, as described here. Activation of neutrophils with phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD. Complete myeloperoxidase (MPO) deficiency can cause a false-positive result for CGD in the DHR flow cytometric assay; however, there is a difference between the % DHR+ neutrophils and the mean fluorescence intensity (MFI) after PMA stimulation that allows discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD neutrophils. It is important to have quantitative measures in the DHR flow cytometry assay to effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimerism and NADPH oxidase activity post-HCT. These quantitative measures include assessment of the relative proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the relative fluorescence intensity of DHR (MFI) on neutrophils after activation. Female carriers of X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome inactivation). Age-related acquired skewing of lyonization can also cause increased susceptibility to infections in carriers of X-linked CGD. While germline mutations are more common in CGD, there have been reports of de novo, sporadic mutations in the CYBB gene, causing X-linked CGD in male patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been reported in patients with X-linked CGD who have small populations of normal cells. There are also reports of triple somatic mosaicism in female carriers as well as late-onset disease in an adult female who was a somatic mosaic for a novel mutation in the CYBB gene. Therefore, the clinical, genetic, and age spectrum of CGD is varied and laboratory assessment of NADPH oxidase activity after neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate diagnosis or for monitoring patients posttransplant.

Useful For: Diagnosis of chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, complete myeloperoxidase (MPO) deficiency; monitoring chimerism and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function posthematopoietic cell transplantation Assessing residual NADPH oxidase activity pretransplant Identification of carrier females for X-linked CGD; assessment of changes in lyonization with age in carrier females

Interpretation: An interpretive report will be provided, in addition to the quantitative values described in Clinical Information. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after phorbol myristate acetate stimulation, and the mean fluorescence intensity. Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease and complete myeloperoxidase deficiency.
Reference Values:

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<tr>
<th>Result Name</th>
<th>Unit</th>
<th>Cutoff for defining normal</th>
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<tr>
<td>% PMA ox-DHR+</td>
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<tr>
<td>MFI PMA ox-DHR+</td>
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Dihydrorhodamine (DHR) Flow Cytometric Test, Blood

Clinical Information: Chronic granulomatous disease (CGD) is caused by genetic defects in the gene components that encode the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. These defects result in an inability to produce superoxide anions required for killing of bacterial and fungal organisms. Other clinical features include a predisposition to systemic granulomatous complications and autoimmunity.(1) There are 5 known genetic defects associated with the clinical phenotype of CGD.(2) The gene defects include mutations in the CYBB gene, encoding the gp91phox protein, which is X-linked and accounts for approximately 70% of CGD cases. Other gene defects are autosomal recessive: NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), and NCF4 (p40phox). Typically, patients with X-linked CGD have the most severe disease, while patients with p40phox defects tend to have the best outcomes. Mutations in NCF4 encoding the p40phox protein have been the most recently described (3) and appears to be associated with more gastrointestinal disease with fewer infections. There is significant clinical variability even among individuals with similar mutations, in terms of NADPH oxidase function, indicating that there can be several modulating factors including the genetic defect, infection history, and granulomatous and autoimmune complications. There appears to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can be treated with hematopoietic cell transplantation (HCT), which can be effective for the inflammatory and autoimmune manifestations. It has been shown that survival of patients with CGD was strongly associated with residual reactive oxygen intermediate (ROI) production, independent of the specific gene defect.(4) Measurement of NADPH oxidase activity through the dihydrorhodamine (DHR) flow cytometry assay...
contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD includes evaluation of NADPH oxidase function in neutrophils, using either the nitroblue tetrazolium test (NBT) or the more analytically sensitive DHR test, as described here. Activation of neutrophils with phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD. Complete myeloperoxidase (MPO) deficiency can cause a false-positive result for CGD in the DHR flow cytometric assay; however, there is a difference between the % DHR+ neutrophils and the mean fluorescence intensity (MFI) after PMA stimulation that allows discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD neutrophils. It is important to have quantitative measures in the DHR flow cytometry assay to effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimerism and NADPH oxidase activity post-HCT. These quantitative measures include assessment of the relative proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the relative fluorescence intensity of DHR (MFI) on neutrophils after activation. This assay can also be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory mutations in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and NADPH oxidase function. Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with PMA, indicating normal NADPH oxidase activity, but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, indicates a signaling defect in Rac2 deficiency. Female carriers of X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome inactivation). Age-related acquired skewing of lyonization can also cause increased susceptibility to infections in carriers of X-linked CGD. While germline mutations are more common in CGD, there have been reports of de novo, sporadic mutations in the CYBB gene, causing X-linked CGD in male patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been reported in patients with X-linked CGD who have small populations of normal cells. There are also reports of triple somatic mosaicism in female carriers as well as late-onset disease in an adult female who was a somatic mosaic for a novel mutation in the CYBB gene. Therefore, the clinical, genetic, and age spectrum of CGD is varied and laboratory assessment of NADPH oxidase activity after neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate diagnosis or for monitoring patients posttransplant.

**Useful For:** Diagnosis of chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, Rac2 deficiency, complete myeloperoxidase (MPO) deficiency; monitoring chimerism and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function posthematopoietic cell transplantation Assessing residual NADPH oxidase activity pretransplant Identification of carrier females for X-linked CGD; assessment of changes in lyonization with age in carrier females

**Interpretation:** An interpretive report will be provided, in addition to the quantitative values. Interpretation of the results of the quantitative dihydorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after phorbol myristate acetate (PMA) and/or N-formyl-methionyl-leucyl-phenylalanine (fMLP) stimulation, and the mean fluorescence intensity (MFI). Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease (CGD) and complete myeloperoxidase (MPO) deficiency.

**Reference Values:**

<table>
<thead>
<tr>
<th>Result Name</th>
<th>Unit</th>
<th>Cutoff for Defining Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% PMA ox-DHR+</td>
<td>%</td>
<td>&gt; or =95%</td>
</tr>
<tr>
<td>MFI PMA ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =60</td>
</tr>
<tr>
<td>% fMLP ox-DHR+</td>
<td>%</td>
<td>&gt; or =10%</td>
</tr>
<tr>
<td>MFI fMLP ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =2</td>
</tr>
<tr>
<td>Control % PMA ox-DHR+</td>
<td>%</td>
<td>&gt; or =95%</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT

**DHTS 81479**

**Dihydrotestosterone, Serum**

**Clinical Information:** The principal prostatic androgen is dihydrotestosterone (DHT). Levels of DHT remain normal with aging, despite a decrease in the plasma testosterone, and are not elevated in benign prostatic hyperplasia (BPH).(1) DHT is generated by reduction of testosterone by 5 alpha-reductase. Two isoenzymes of 5 alpha-reductase have been discovered. Type 1 is present in most tissues in the body where 5 alpha-reductase is expressed, and is the dominant form in sebaceous glands. Type 2 is the dominant isoenzyme in genital tissues, including the prostate. Androgenetic alopecia (AGA; male-pattern baldness) is a hereditary and androgen-dependent progressive thinning of the scalp hair that follows a defined pattern.(2) While the genetic involvement is pronounced but poorly understood, major advances have been achieved in understanding the principal elements of androgen metabolism that are involved. DHT may be related to baldness. High concentrations of 5 alpha-reductase have been found in frontal scalp and genital skin and androgen-dependent processes are predominantly due to the binding of DHT to the androgen receptor (AR). Since the clinical success of treatment of AGA with modulators of androgen metabolism or hair growth promoters is limited, sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of AGA. Currently available AGA treatment modalities with proven efficacy are oral finasteride, a competitive inhibitor of 5 alpha-reductase type 2, and topical minoxidil, an adenosine triphosphate-sensitive potassium channel opener that has been reported to stimulate the production of vascular endothelial growth factor in cultured dermal papilla cells. Currently, many patients with prostate disease receive treatment with a 5 alpha-reductase inhibitor such as finasteride (Proscar) to...
diminish conversion of DHT from testosterone. See Steroid Pathways in Special Instructions.

**Useful For:** Monitoring patients receiving 5 alpha-reductase inhibitor therapy or chemotherapy
Evaluating patients with possible 5 alpha-reductase deficiency

**Interpretation:** Patients taking 5 alpha-reductase inhibitor have decreased dihydrotestosterone (DHT) serum levels. Patients with genetic 5 alpha-reductase deficiency (a rare disease) also have reduced DHT serum levels. DHT should serve as the primary marker of peripheral androgen production. However, because it is metabolized rapidly and has a very high affinity for sex hormone-binding globulin (SHBG), DHT does not reflect peripheral androgen action. Instead, its distal metabolite, 3 alpha, 17 beta-androstanediol glucuronide, serves as a better marker of peripheral androgen action See Steroid Pathways in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Mean Age</th>
<th>Reference Range (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;6 months and prepubertal) 7.1 years</td>
<td>&lt; or =50</td>
</tr>
<tr>
<td>Stage II 12.1 years</td>
<td>&lt; or =200</td>
</tr>
<tr>
<td>Stage III 13.6 years</td>
<td>80-330</td>
</tr>
<tr>
<td>Stage IV 15.1 years</td>
<td>220-520</td>
</tr>
<tr>
<td>Stage V 18 years</td>
<td>240-650 &gt;19 years: 112-955 pg/mL Females Cord blood: &lt; or =50 pg/mL &lt; or =6 months: &lt; or =1,200 pg/mL Tanner Stages</td>
</tr>
</tbody>
</table>


Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a
patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC). DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias, and conduction system disease, or thromboembolic disease (stroke). The most recent estimates of the incidence of DCM suggest that the condition affects approximately 1 in every 250 people. These estimates are higher than originally reported due to subclinical phenotypes and underdiagnosis. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. The majority of familial dilated cardiomyopathy is inherited in an autosomal dominant manner; however, autosomal recessive and X-linked forms have also been reported. At least 28 genes have been reported in association with DCM, including genes encoding the cardiac sarcomere and other proteins involved in proteins responsible for cardiac muscle contraction. Some genes associated with DCM also cause other forms of hereditary cardiomyopathy, cardiac channelopathies, skeletal myopathies, or metabolic defects. See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Dilated Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ABCC9 ATP-Binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKRD1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM, CRYAB Crystallin, alpha-B AD, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD HCM, DCM, DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, Neurogenic Scapuloperoneal Syndrome Kaeser Type, LGMD LAMA4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated membrane protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MYBPC3 Myosin-binding protein-C, cardiac AD HCM, DCM, MYH6 Myosin, heavy chain 6, cardiac muscle, alpha HCM, DCM, MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYPN Myopalladin AD HCM, DCM, NEXN Nexilin AD HCM, DCM PLN Phospholamban AD HCM, DCM RAF1 V-raf-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome, DCM RLM20 RNA-binding motif protein 20 AD DCM SCN5A Sodium channel, voltage gated, type V, alpha subunit AD Brugada syndrome, DCM, Heart block, LQTS, SSS, SIDS SGCD Sarcoglycan, delta AD, AR DCM, LGMD TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TCAP Titin-CAP (Telethonin) AD, AR DCM, LGMD TNNC1 Troponin C, slow AD HCM, DCM TNNT1 Troponin I, cardiac AD, AR DCM, AR, DCM, RCM TMNT2 Troponin T2, cardiac AD HCM, DCM, RCM, LVNC TPM1 Troponymosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, ARVC myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), congenital heart defects (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary dilated cardiomyopathy (DCM) Establishing a diagnosis of a hereditary DCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identification of a pathogenic variant within a gene known to be associated with disease features that allows for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical
judgment.

**Reference Values:**
An interpretive report will be provided.


**Dill, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Diltiazem (Cardizem, Dilacor)
Reference Values:
Reference Range: 50 - 200 ng/mL

Dilute Russell Viper Venom Time (DRVVT) Confirmation Ratio
Reference Values:
Only orderable as part of a profile. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma and DRVVTJ / Dilute Russell Viper Venom Time (DRVVT) Mix and Confirm Reflexes, Plasma.

<1.2
Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Dilute Russell Viper Venom Time (DRVVT) Interpretation
Reference Values:
Only orderable as a part of a reflex. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma.

Dilute Russell Viper Venom Time (DRVVT) Mix Ratio
Reference Values:
Only orderable as part of a profile. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma and DRVVTJ / Dilute Russell Viper Venom Time (DRVVT) Mix and Confirm Reflexes, Plasma.

<1.2
Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma
Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more
phospholipid-dependent clotting time tests (e.g., activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (e.g., lupus sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation testing is recommended, including the prothrombin time (PT), APTT, thrombin time (TT), and the DRVVT. If the PT, APTT, or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine the presence or absence of anticoagulants or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from the Russell viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests that have a higher phospholipid content (e.g., LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm the presence of LA or to help exclude LA. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.2) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.2) are subjected to reflexive testing (DRVVT mix and confirmation ratios) as described in the Testing Algorithm (also see Interpretation). It is advisable to use the DRVVT screen, mix, and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Detecting and confirming or helping to exclude the presence of lupus anticoagulants (LA) Excluding LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.2): A normal DRVVT screen ratio (<1.2) indicates that lupus anticoagulants (LA) is not present, or not detectable, by this method (but might be detected with other methods). Abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.2) may suggest the presence of LA; however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired. -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.2) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.2) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirm ratios). Possible combinations of results include the following: -DRVVT screen ratio > or =1.2 and DRVVT mix ratio <1.2 DRVVT confirm ratio <1.2: No evidence of LA. This data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.2 and DRVVT mix ratio > or =1.2 DRVVT confirm ratio <1.2: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (e.g., factor V inhibitor), anticoagulation therapy effects, or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease, etc. Although LA cannot be conclusively excluded, the DRVVT confirm ratio of <1.2 makes this less likely. -DRVVT screen ratio > or =1.2 and DRVVT mix ratio <1.2 DRVVT confirm ratio > or =1.2: Although mixing study of the prolonged DRVVT (DRVVT screen and mix ratios) provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirm ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.2 and DRVVT mix ratio > or =1.2 DRVVT confirm ratio > or =1.2: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions). Because no single coagulation test can identify or exclude all LAs, and because of the
complexity of testing LA, a combination or panel of coagulation tests is recommended: LUPPR / Lupus Anticoagulant Profile THRMP / Thrombophilia Profile PROCT / Prolonged Clot Time Profile DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

**Reference Values:**
Dilute Russell viper venom time screen ratio <1.2
Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

**Clinical References:**
6. CLSI Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A.

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**Diphtheria Toxoid IgG Antibody, Serum**

**Clinical Information:** Diphtheria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx and posterior nasal passages. Corynebacterium diphtheriae produces a potent diphtheria exotoxin which is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diphtheria toxoid, which stimulates anti-diphtheria toxoid antibodies. In the United States, diphtheria toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (Tdap) vaccine. A patient’s immunological response to diphtheria toxoid vaccination can be determined by measuring anti-diphtheria toxoid IgG antibody using this enzyme immunoassay technique. An absence of antibody formation post-vaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

**Useful For:**
Determining a patient’s immunological response to diphtheria toxoid vaccination

**Interpretation:**
Results > or =0.01 IU/mL suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with anti-diphtheria toxoid IgG values between 0.01 and <0.1 IU/mL.

**Reference Values:**
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)

**Clinical References:**

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**Diphtheria/Tetanus Antibody Panel, Serum**
Clinical Information: Diphtheria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx and posterior nasal passages. Corynebacterium diphtheriae produces a potent diphtheria exotoxin which is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diphtheria toxoid, which stimulates anti-diphtheria toxoid antibodies. In the United States, diphtheria toxoid is administered to children as part of the combined diphtheria, tetanus, acellular pertussis (TdaP) vaccine. A patient’s immunological response to diphtheria toxoid vaccination can be determined by measuring anti-diphtheria toxoid IgG antibody using this enzyme immunoassay technique. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs. Diphtheria results from contamination of wounds or lacerations with Corynebacterium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin, tetanospsamin. Tetanospsamin attaches to peripheral nerve endings and travels to the central nervous system (CNS) where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospsamin), which stimulates development of anti-tetanus toxoid antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, acellular pertussis (TdaP) vaccine. Two to three weeks following vaccination, a patient's immunological response may be assessed by measuring the total anti-tetanus toxoid IgG antibody level in serum. An absence of antibody formation post-vaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Assessment of an antibody response to tetanus and diphtheria toxoid vaccines An aid to diagnose immunodeficiency

Interpretation: Diphtheria: Results > or =0.01 IU/mL suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with anti-diphtheria toxoid IgG values between 0.01 and <0.1 IU/mL. Tetanus: Results > or =0.01 IU/mL suggest a vaccine response. A tetanus toxoid booster should strongly be considered for patients with anti-tetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients who have a measurable serum level of 0.01 to 1.0 IU/mL.

Reference Values:
DIPHTHERIA TOXOID IgG ANTIBODY
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)

TETANUS TOXOID IgG ANTIBODY
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)


FDIPY 90371 Dipyridamole, Serum/Plasma
Reference Values:
Reporting limit determined each analysis

Synonym(s): Persantine

Steady-state trough plasma concentrations following a three times daily regimen of:

- 50 mg: 0.1 - 1.5 mcg/mL
- 75 mg: 0.1 - 2.6 mcg/mL

Direct Coombs, Blood

Clinical Information: IgG antibody or complement components secondary to the action of IgM antibody may be present on the patient’s own RBCs or on transfused RBCs.

Useful For: Demonstrating in vivo coating of RBCs with IgG or the complement component C3d in the following settings: -Autoimmune hemolytic anemia -Hemolytic transfusion reactions -Drug-induced hemolytic anemia

Interpretation: Negative: no IgG antibody or complement (C3d) detected on the surface of the red cell. Positive: IgG or complement (C3d) is present on the surface of the red cell.

Reference Values:
Negative
If positive, reaction is graded (micro positive to 4+).


Disaccharidase Analysis

Reference Values:
Lactase: Range 24.5 +/- 8.0
Abnormal <15.0

Units = uM/min/gram protein

Sucrase: Range 54.4 +/- 25.4
Abnormal <25.0

Units = uM/min/gram protein

Maltase: Range 160.8 +/- 62.8
Abnormal <100.0

Units = uM/min/gram protein

Palatinase: Range 11.1 +/- 6.5
Abnormal <5.0

Units = uM/min/gram protein

Disaccharidase Panel

Reference Values:
3%ile 10%ile mean s.d. n
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
<th>Value 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactase</td>
<td>15.4</td>
<td>17.0</td>
<td>33.4</td>
<td>16.4</td>
<td>1,213</td>
</tr>
<tr>
<td>Maltase</td>
<td>103.7</td>
<td>120.0</td>
<td>213.3</td>
<td>87.6</td>
<td>1,715</td>
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<tr>
<td>Sucrase</td>
<td>28.7</td>
<td>33.9</td>
<td>63.9</td>
<td>28.0</td>
<td>1,734</td>
</tr>
<tr>
<td>Palatinase</td>
<td>8.6</td>
<td>10.0</td>
<td>16.4</td>
<td>6.0</td>
<td>1,734</td>
</tr>
<tr>
<td>Glucoamylase</td>
<td>24.6</td>
<td>27.4</td>
<td>48.7</td>
<td>18.2</td>
<td>66</td>
</tr>
</tbody>
</table>

*data from normal patients Units=uM/min/gram protein*  

**Interpretation:**

Double-stranded (dsDNA) antibodies are known to fluctuate with disease activity in lupus erythematosus, often increasing prior to an increase in inflammation and decreasing in response to therapy. See Connective Tissue Diseases Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms consistent with systemic lupus erythematosus (SLE)

**Interpretation:** A positive test result for double-stranded DNA (dsDNA) antibodies is consistent with...

---

**FDIRU 57280**  
**Diuretic Screen, Urine**

**Reference Values:**

Qualitative diuretic screen includes: benzthiazide, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, hydroflumethiazide, and metolazone.

**FDMZ 57859**  
**DM2 DNA Test**

**Reference Values:**

A final report will be attached in MayoAccess.

**FDM1 91592**  
**DMPK DNA Test (DM1)**

**Reference Values:**

A final report will be attached in MayoAccess.

**CRITH 62925**  
**DNA Double-Stranded (dsDNA) Antibodies by Crithidia luciliae IFA, IgG, Serum**

**Reference Values:**

Only orderable as reflex. For more information see ADNAR / DNA Double-Stranded (dsDNA) Antibodies with Reflex, IgG, Serum.

**ADNAR 63073**  
**DNA Double-Stranded (dsDNA) Antibodies with Reflex, IgG, Serum**

**Clinical Information:** Double-stranded (ds, native) DNA (dsDNA) antibodies of the IgG class are an accepted criterion (American College of Rheumatology) for the diagnosis of systemic lupus erythematosus (SLE).(1-3) dsDNA antibodies are detectable in approximately 85% of patients with untreated SLE, and are rarely detectable in other connective tissue diseases. Weakly positive results caused by low-avidity antibodies to dsDNA are not specific for SLE and can occur in a variety of diseases. Testing for IgG antibodies to dsDNA is indicated in patients who have a positive test for antinuclear antibodies (ANA) along with signs and symptoms that are compatible with the diagnosis of SLE.(2) If the ANA test is negative, there is no reason to test for antibodies to dsDNA.(2) The levels of IgG antibodies to dsDNA in serum are known to fluctuate with disease activity in lupus erythematosus, often increasing prior to an increase in inflammation and decreasing in response to therapy.(1,2) See Connective Tissue Diseases Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms consistent with systemic lupus erythematosus (SLE)

**Interpretation:** A positive test result for double-stranded DNA (dsDNA) antibodies is consistent with...
the diagnosis of systemic lupus erythematosus. A reference range study conducted at the Mayo Clinic demonstrated that, within a cohort of healthy adults (n=120), no individuals between the ages of 18 and 60 (n=78) had detectable anti-dsDNA antibodies. Above the age of 60 (n=42), 11.9% of individuals (n=5) had a borderline result for dsDNA antibodies and 4.8% of individuals (n=2) had a positive result.

Reference Values:
<30.0 IU/mL (negative)
30.0-75.0 IU/mL (borderline)
>75.0 IU/mL (positive)
Negative is considered normal.
Reference values apply to all ages.

Dock Yellow (Rumex crispus) IgE

**Interpretation:** Class IgE (kU/L) Comment
- 0 < 0.10 Negative
- 0.10 - 0.34 Equivocal
- 0.35 - 0.69 Low Positive
- 0.70 - 3.4 Moderate Positive
- 3.5 - 17.4 High Positive
- 17.5 - 49.9 Very High Positive
- 50.0 - 99.9 Very High Positive
- > or = 100 Very High Positive

**Reference Values:**
<0.35 kU/L

Dog Dander, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Dopamine Receptor D3 Genotype**

**Clinical Information:** The neurotransmitter dopamine acts via dopamine receptors in the central nervous system. Dopamine receptor subtypes D1 through 5 (DRD1-5) are of interest in schizophrenia research because many of the antipsychotic drugs interact with and block 1 or several of these receptors. There has been a strong association between DRD2 receptor blockade and antipsychotic drug dose for typical antipsychotics (eg, haloperidol, chlorpromazine). However, this association has not been maintained for the atypical antipsychotics (eg, clozapine, risperidone). The atypical antipsychotic medications have high binding affinity for the polymorphic DRD3 receptor. For DRD3, a single nucleotide change (DRD3 25A->G) results in an amino acid coding polymorphism, Ser9Gly, which is associated with variable response to treatment with atypical antipsychotic medications and predisposition to tardive dyskinesia, a side effect of certain antipsychotic drugs. Worldwide, the frequency of the A (DRD3 25A) and G (DRD3 25G) alleles is nearly equal. However, the allele frequencies are markedly different in different populations (see below) and this may impact the risk of tardive dyskinesia within a given population or cohort following treatment with antipsychotic drugs. Population Frequencies for DRD3 25A and DRD3 25G alleles: - Allele frequency - European: G=35%, A=65% - African American: G=70%, A=30% - Han Chinese Beijing: G=37%, A=63% - Japanese: G=24%, A=76% Other polymorphisms in the 5’ promoter region of DRD3 have also been studied, but results are too preliminary to be used in the management or diagnoses of psychiatric illnesses. Tardive dyskinesia: The DRD3 25G polymorphism is associated with the presence and severity of typical neuroleptic-induced tardive dyskinesia in schizophrenic patients. Higher mean movement scores were found in patients homozygous for the DRD3 25G allele as compared to both heterozygous and DRD3 25A homozygous patients. (1, 2) The risk for tardive dyskinesia increases with the number of DRD3 25G alleles. Individuals homozygous for the DRD3 25G allele have an odds ratio of 2.8 for developing tardive dyskinesia compared to individuals homozygous for the DRD3 25A allele. (2) Treatment responses: The DRD3 25G allele has been associated with treatment response to clozapine (3) and olanzapine. Among a group of Chinese patients with schizophrenia treated with risperidone, patients homozygous for the DRD3 25A allele had a better response, as measured by improved scores on the Positive and Negative Symptom Scale (PANSS), a questionnaire used to evaluate symptoms associated with schizophrenia, compared to patients homozygous for the DRD3 25G allele. (4) These improved responses included decreased social and emotional withdrawal, improved abstract thinking, and increased spontaneity and flow of conversation. A better response was observed in the heterozygous state (DRD3 25AG) compared to the homozygous groups (DRD3 25GG, P=0.05; DRD3 25AA P=0.06) in another study of patients receiving a variety of typical and atypical antipsychotics. (5)

**Useful For:** Influencing choice of antipsychotics prior to treatment, especially to ascertain if atypical antipsychotics may be used with low risk of tardive dyskinesia. Identifying those patients receiving antipsychotics who are at increased risk of developing tardive dyskinesias. Individuals with the 25G allele should be monitored closely for signs of tardive dyskinesia if a decision is made to treat with antipsychotics. Testing may also be considered for individuals who will receive antipsychotic medications, if they are first-degree relatives of patients who have developed tardive dyskinesia. Assessing potential for effective treatment response with clozapine, olanzapine, and risperidone.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**DRD3O**

**Dopamine Receptor D3 Genotype, Saliva**

**Clinical Information:** The neurotransmitter dopamine acts via dopamine receptors in the central nervous system. Dopamine receptor subtypes D1 through 5 (DRD1-5) are of interest in schizophrenia research because many of the antipsychotic drugs interact with and block 1 or several of these receptors. There has been a strong association between DRD2 receptor blockade and antipsychotic drug dose for typical antipsychotics (eg, haloperidol, chlorpromazine). However, this association has not been maintained for the atypical antipsychotics (eg, clozapine, risperidone). The atypical antipsychotic medications have high binding affinity for the polymorphic DRD3 receptor. For DRD3, a single nucleotide change (DRD3 25A->G) results in an amino acid coding polymorphism, Ser9Gly, which is associated with variable response to treatment with atypical antipsychotic medications and predisposition to tardive dyskinesia, a side effect of certain antipsychotic drugs. Worldwide, the frequency of the A (DRD3 25A) and G (DRD3 25G) alleles is nearly equal. However, the allele frequencies are markedly different in different populations (see below) and this may impact the risk of tardive dyskinesia within a given population or cohort following treatment with antipsychotic drugs. Population Frequencies for DRD3 25A and DRD3 25G Alleles: -Allele frequency - European: G=35%, A=65% - African American: G=70%, A=30% - Han Chinese Beijing: G=37%, A=63% - Japanese: G=24%, A=76% Other polymorphisms in the 5' promoter region of DRD3 have also been studied, but results are too preliminary to be used in the management or diagnoses of psychiatric illnesses. Tardive dyskinesia: The DRD3 25G polymorphism is associated with the presence and severity of typical neuroleptic-induced tardive dyskinesia in schizophrenic patients. Higher mean movement scores were found in patients homozygous for the DRD3 25G allele as compared to both heterozygous and DRD3 25A homozygous patients. The risk for tardive dyskinesia increases with the number of DRD3 25G alleles. Individuals homozygous for the DRD3 25G allele have an odds ratio of 2.8 for developing tardive dyskinesia compared to individuals homozygous for the DRD3 25A allele. Treatment responses: The DRD3 25G allele has been associated with treatment response to clozapine and olanzapine. Among a group of Chinese patients with schizophrenia treated with risperidone, patients homozygous for the DRD3 25A allele had a better response, as measured by improved scores on the Positive and Negative Symptom Scale (PANSS), compared to patients homozygous for the DRD3 25G allele. These improved responses included decreased social and emotional withdrawal, improved abstract thinking, and increased spontaneity and flow of conversation. A better response was observed in the heterozygous state (DRD3 25AG) compared to the homozygous groups (DRD3 25GG, P=0.05; DRD3 25AA P=0.06) in another study of patients receiving a variety of typical and atypical antipsychotics.

**Useful For:** Influencing choice of antipsychotics prior to treatment, especially to ascertain if atypical antipsychotics may be used with low risk of tardive dyskinesia Identifying those patients receiving antipsychotics who are at increased risk of developing tardive dyskinesias. Individuals with the 25G allele should be monitored closely for signs of tardive dyskinesia if a decision is made to treat with antipsychotics. Testing may also be considered for individuals who will receive antipsychotic medications, if they are first-degree relatives of patients who have developed tardive dyskinesia. Assessing potential for effective treatment response with clozapine, olanzapine, and risperidone Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report will be provided.

**Reference Values:**

An interpretive report will be provided.

Dopamine Receptor D4 Genotype (DRD4), Blood

Clinical Information: The dopamine receptor D4 gene (DRD4) is located near the telomeric region of chromosome 11q and is a highly variable gene. A 48-base pair (bp) variable number tandem repeat polymorphism in exon 3 of DRD4, which ranges from 2 to 11 repeats, creates a 32- to 176-amino acid variation in the third intracellular loop on the dopamine receptor. The frequency of these alleles is shown in the table. The DRD4 7-repeat allele (7R) has functional consequences and is associated with lower affinity for dopamine receptor agonists and reduced signal transduction (eg, cAMP levels) compared to the more common DRD4 4-repeat allele (4R). The effect of other copy number repeats is not as well defined to date. Frequency of alleles with various DRD4 exon 3 48-bp repeats: Allele/Number of repeats (R) Allelic Frequency (%) 2R 8.8 3R 2.4 4R 65.1 5R 1.6 6R 2.2 7R 19.2 8R 0.6 9R <0.1 10R <0.1 11R <0.1 The DRD4 protein is expressed in a number of brain regions, with higher levels of expression in the prefrontal cortex, where animal models suggest that it inhibits neuronal firing. Attention Deficit/Hyperactivity Disorder (ADHD): Several studies have found associations between the DRD4 7R allele and ADHD.(1,2) Similarly, a long form (240-bp variant) of a DRD4 promoter repeat polymorphism is associated with ADHD susceptibility, possibly due to linkage disequilibrium with the DRD4 7R allele.(3) Pharmacogenetics: Several studies demonstrate that the presence of the DRD4 7R allele, alone or in combination with the SLC6A4 long/long promoter polymorphism of the serotonin transporter, is associated with lower responsiveness of ADHD to methylphenidate (eg, Ritalin, Concerta), the main treatment for ADHD.(4) Methylphenidate dosage may have to be increased to effectively treat individuals with the DRD4 7R allele. The effect of other repeat numbers has not been defined to date and, if other alleles than the 4R and 7R are present, caution should be exercised in using methylphenidate to treat ADHD because the impact of these alleles on treatment response is not known. Attempts to find an association between DRD4 genotype and the variability of response to antipsychotic drugs, especially clozapine, have been largely unsuccessful or have yielded conflicting results.

Useful For: Influencing the target dose of methylphenidate treatment for patients with attention deficit/hyperactivity disorder Determining possible cause for poor response to methylphenidate in treated patients with attention deficit/hyperactivity disorder

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


Dopamine Receptor D4 Genotype (DRD4), Saliva

Clinical Information: The dopamine receptor D4 gene (DRD4) is located near the telomeric region of chromosome 11q and is a highly variable gene. A 48-base pair (bp) variable number tandem repeat...
(VNTR) polymorphism in exon 3 of DRD4, which ranges from 2 to 11 repeats, creates a 32- to 176-amino acid variation in the third intracellular loop on the dopamine receptor. The frequency of these alleles is shown in Table 1. The DRD4 7-repeat allele (7R) has functional consequences and is associated with lower affinity for dopamine receptor agonists and reduced signal transduction (eg, cAMP levels) compared to the more common DRD4 4-repeat allele (4R). The effect of other copy number repeats is not as well defined to date, however, and VNTRs with 6 or fewer repeats are grouped as 4R and those with 7 or more repeats as 7R. Frequency of alleles with various DRD4 exon 3 48-bp repeats: Allele/Number of Repeats (R) Allelic Frequency (%) 2R 8.8 3R 2.4 4R 65.1 5R 1.6 6R 2.2 7R 19.2 8R 0.6 9R <0.1 10R <0.1 11R <0.1 The DRD4 protein is expressed in a number of brain regions, with higher levels of expression in the prefrontal cortex, where animal models suggest that it inhibits neuronal firing. Attention Deficit/Hyperactivity Disorder (ADHD): Several studies have found associations between the DRD4 7R allele and ADHD. (1,2) Similarly, a long form (240-bp variant) of a DRD4 promotor repeat polymorphism is associated with ADHD susceptibility, possibly due to linkage disequilibrium with the DRD4 7R allele. (3) Pharmacogenetics: Several studies demonstrate that the presence of the DRD4 7R allele, alone or in combination with the SLC6A4 long/long promotor polymorphism of the serotonin transporter, is associated with lower responsiveness of ADHD to methylphenidate (eg, Ritalin, Concerta), the main treatment for ADHD. (4) Methylphenidate dosage may have to be increased to effectively treat individuals with the DRD4 7R allele. Attempts to find an association between DRD4 genotype and the variability of response to antipsychotic drugs, especially clozapine, have been largely unsuccessful or have yielded conflicting results.

**Useful For:** Influencing the target dose of methylphenidate treatment for patients with attention deficit/hyperactivity disorder Determining possible cause for poor response to methylphenidate in treated patients with attention deficit/hyperactivity disorder Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Douglas Fir, IgE**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5–49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0–99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Doxepin and Nordoxepin, Serum**

**Clinical Information:** Doxepin is recommended for the treatment of psychoneurotic patients with depression or anxiety, and depression or anxiety associated with alcoholism or organic disease. Nordoxepin (N-desmethyldoxepin) is the major metabolite and is usually present at concentrations equal to doxepin. Optimal efficacy occurs at combined serum concentrations between 50 and 150 ng/mL. Like other tricyclic antidepressants, the major toxicity of doxepin is expressed as cardiac dysrythmias, which occur at concentrations in excess of 300 ng/mL. Other side effects include nausea, hypotension, and dry mouth.

**Useful For:** Monitoring therapy Evaluating potential toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to doxepin when combined serum levels of doxepin and nordoxepin are between 50 and 150 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels > or =300 ng/mL. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

Therapeutic concentration (doxepin + nordoxepin): 50-150 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Drug Abuse Panel with Confirmation, Chain of Custody, Urine

Clinical Information: This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS), gas chromatography-flame ionization detection (GC-FID), or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the following drugs: -Amphetamines -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Opiates -Phencyclidine -Tetrahydrocannabinol Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, marijuana, opiates, and phencyclidine This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg. AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html

Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoyllecgonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


Drug Abuse Survey with Confirmation, Panel 5, Chain of Custody, Urine

Clinical Information: This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the following drugs: -Amphetamines -Cocaine -Opiates -Phencyclidine -Tetrahydrocannabinol Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detecting drug abuse involving amphetamines, cocaine, marijuana, opiates, and phencyclidine This chain-of-custody test is intended to be used in a setting where the test results can be
Reference Values:

Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References:
Custody, Urine

**Clinical Information:** This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the most common classes of drugs of abuse. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS (positive alcohol by GC) or LC-MS/MS and quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html

**Reference Values:**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Cutoff Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>500 ng/mL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>200 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>100 ng/mL</td>
</tr>
<tr>
<td>Cocaine (benzoylcegonine-cocaine metabolite)</td>
<td>150 ng/mL</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10 mg/dL</td>
</tr>
<tr>
<td>Methadone metabolite</td>
<td>300 ng/mL</td>
</tr>
<tr>
<td>Opiates</td>
<td>300 ng/mL</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>25 ng/mL</td>
</tr>
<tr>
<td>Tetrahydrocannabinol carboxylic acid</td>
<td>50 ng/mL</td>
</tr>
</tbody>
</table>

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


Drug Abuse Survey with Confirmation, Panel 9, Urine

**Clinical Information:** This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the most common classes of drugs of abuse. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS (positive alcohol by GC) or LC-MS/MS, and quantitated, before a positive result is reported. This test represents the coupling of UDOA / Drug Abuse Survey, Urine with an automatic confirmation of all positive results by the definitive assay available and described elsewhere (eg, AMPHU / Amphetamines Confirmation, Urine).

**Useful For:** Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.
Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylecgogine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


Drug Abuse Survey with Confirmation, Urine

Clinical Information: This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS), gas chromatography-flame ionization detection (GC-FID), or liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the following drugs:
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Ethanol
- Opiates
- Phencyclidine
- Tetrahydrocannabinol
This assay represents the coupling of UDOA / Drug Abuse Survey, Urine with an automatic confirmation of all positive results by the definitive assay available and described elsewhere (eg, AMPHU / Amphetamines, Urine). All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS and quantitated, before a positive result is reported. Some drug treatment programs do not require confirmatory testing of screen-positive specimens. In those settings, UDOA / Drug Abuse Survey, Urine is a less costly option. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, marijuana, opiates, and phencyclidine This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHU / Amphetamines, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html

Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


DAU
501040

Drug of Abuse Screen, DAU10, Urine

Clinical Information: This test uses immunologic testing for drugs of abuse, by class, and screens for the presence of amphetamines, barbiturates, benzodiazepines, cocaine metabolite, methadone, opiates, phencyclidine, tetrahydrocannabinol, and ethanol. Positive immunologic results are confirmed by gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry with the exception of ethanol. Positive ethanol results are reported quantitatively directly from immunologic testing.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinol, and ethanol. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, DAUAM / Drugs of Abuse, Amphetamines GC-MS Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html Creatinine and specific gravity are measured as indicators of specimen dilution.

Reference Values:
Negative
The specific drug identified will be reported.

Enzyme-multiplied immunoassay technique cutoff concentrations:
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 200 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Methadone: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
Ethanol: 10 mg/dL
Results of this test are confirmed and should be considered definitive.


DAAMP
505341

Drug of Abuse, Amphetamine Screen with GC-MS Confirmation, Urine

Clinical Information: Amphetamines are sympathomimetic amines that stimulate central nervous system activity and, in part, suppress appetite. Phentermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All of the other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of...
narcolepsy, attention-deficit disorder/attention-deficit hyperactive disorder, and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

**Useful For:** Confirming drug abuse involving amphetamines such as amphetamine and methamphetamine, phentermine, methylenedioxyethylamphetamine (MDEA), and methylene-diaxyethylamphetamine (MDA, a metabolite of MDMA and MDEA)

**Interpretation:** The presence of amphetamines in urine concentrations >500 ng/mL is a strong indicator that the patient has used these drugs within the past 3 days. This test is very specific and does not produce a false-positive result when over-the-counter drugs are present in the specimen. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (which contain amphetamine); Desoxy n and Vicks Inhaler (which contain methamphetamine); Selegiline (metabolizes to methamphetamine and amphetamine); and clobenzorex, famprofazone, fenethylline, fenproporex, and mfenorex (which are amphetamine pro-drugs).

**Reference Values:**

- Negative
  - EMIT cutoff concentration: 500 ng/mL
  - Positives are reported with a quantitative GC/MS result.

**Clinical References:** Baselt RC, Cravey RH: Disposition of Toxic Drugs and Chemicals in Man. Third edition. Chicago, Year Book Medical Publishers, 1989

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**Drug of Abuse, Barbiturate Screen with GC-MS Confirmation, Urine**

**Clinical Information:** Barbiturates constitute a class of central nervous system depressants. They are classified on their duration of action. The duration of action is approximately 15 minutes for the short-acting types (eg, secobarbital and pentobarbital), and a day or more for the long-acting types (eg, phenobarbital). Short-acting barbiturates are usually excreted in the urine as metabolites, while the long-acting barbiturates appear primarily unchanged. Barbiturates were originally introduced as sleep inducers. Butalbital also is used to control severe headaches. Mephobarbital and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as "downers" to induce sleep after an amphetamine- or cocaine-induced "high."

**Useful For:** Screening and confirming drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital.

**Interpretation:** The presence of barbiturate in urine at >199 ng/mL indicates use of one of these drugs. Most barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

**Reference Values:**

- Negative
  - Positives are reported with a quantitative GC-MS result.
  - EMIT cutoff concentration: 200 ng/mL.

**Clinical References:** Baselt RC, Cravey RH: Disposition of Toxic Drugs and Chemicals In Man. Third edition. Chicago, IL Year Book Medical Publishers, 1989

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**Drug of Abuse, Benzodiazepine Screen with GC-MS Confirmation, Urine**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 681
**Clinical Information:** Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most commonly prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents.

**Useful For:** Detecting drug use involving benzodiazepines such as alprazolam, flunitrazepam, chlordiazepoxide, diazepam, flurazepam, lorazepam, and triazolam

**Interpretation:** Benzodiazepines are extensively metabolized and the parent compounds are not detected in urine. This test provides screening and confirmation for the presence of: -Nordiazepam, oxazepam (metabolites of chlordiazepoxide) -Nordiazepam, oxazepam and temazepam (metabolites of diazepam) -Lorazepam -Hydroxyethylflurazepam (metabolite of flurazepam) -Alpha hydroxyalprazolam (metabolite of alprazolam) -Alpha hydroxytriazolam (metabolite of triazolam) -7-Aminoclonazepam (metabolite of clonazepam) -7-Aminoflunitrazepam (metabolite of flunitrazepam) The clearance half-life of long-acting benzodiazepines is >24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5-day to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Medical Laboratories Drugs of Abuse Testing Guide at http://www.mayomedicallaboratories.com/articles/drug-book/index.html for additional information including metabolism, clearance (half-life), and approximate detection times.

**Reference Values:**
Negative
EMIT cutoff concentration: 200 ng/mL
Positives are reported with a quantitative GC/MS result.

**Clinical References:**
Chromatography-Tandem Mass Spectrometry (LC-MS/MS), Urine

**Clinical Information:** Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin. (1) Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6. (1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved. (1-5) Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). (1-4) The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys. (1,4) Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH. (5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy. (5) Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine. (6) This is commonly referred to as "spiking." In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP. (6) The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen.

**Useful For:** Monitoring of methadone treatment for analgesia or drug rehabilitation Assessing compliance with rehabilitation programs, particularly urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine

**Interpretation:** The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of >0.60. (7) An EDDP:methadone ratio <0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen. (6)

**Reference Values:**

- Negative
  - EMIT cutoff concentration: 300 ng/mL
  - Positives are reported with a quantitative result.

Drug of Abuse, Opiates Confirmation, Urine

Clinical Information: Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2,000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6 beta hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6 hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for the opiates is generally 2 to 3 days after last ingestion.

Useful For: Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, and oxymorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:

Negative
Positive cutoff concentrations
Codeine: <100 ng/mL
Hydrocodone: <100 ng/mL
Hydromorphone: <100 ng/mL
Morphine: <100 ng/mL
Oxycodone: <100 ng/mL
Oxymorphone: <100 ng/mL


Drug of Abuse, Phencyclidine Screen With GC-MS Confirmation, Urine

Clinical Information: Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotonergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, giving bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screen. PCP is...
excreted in the urine.

**Useful For:** Detection of drug abuse involving phencyclidine (angel dust or angel hair)

**Interpretation:** The presence of phencyclidine (PCP) in urine at concentrations >10 ng/mL is a strong indicator that the patient has used PCP.

**Reference Values:**
Negative
EMIT cutoff concentration: 25 ng/mL
Positives are reported with a quantitative GC-MS result.

**Clinical References:** Baselt RC: In Disposition of Toxic Drugs and Chemicals in Man, Fifth edition. Chemical Toxicology Institute, Foster City, CA 2000

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**Drug of Abuse, Tetrahydrocannabinol Screen with GC-MS Confirmation, Urine**

**Clinical Information:** Marijuana is 1 of the most widely abused drugs in the United States. It is the term for describing a leafy preparation of the plant Cannabis sativa used to produce psychic effects. A common method for the consumption of marijuana is smoking. The primary component of marijuana is delta-9-tetrahydrocannabinoid (THC). It is the concentration of THC that determines the potency of marijuana. Following consumption of the drug, either by inhalation or ingestion, THC is rapidly metabolized by the liver through 11-hydroxy-delta-9-THC to a series of polar metabolites, with 11-nor-delta-9-THC-alpha-carboxylic acid (THC carboxylic acid, THC-COOH) being the primary metabolite. Approximately 80% of a dose of THC is eliminated during the first 5 days, with >65% being excreted in feces and approximately 20% excreted in urine. Depending on assay sensitivity, cannabinoid metabolites may be detected in the urine up to 10 days in occasional smokers and 30 to 40 days in chronic smokers.

**Useful For:** Detection and confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana)

**Interpretation:** The metabolite of marijuana (delta-9-tetrahydrocannabinoid-carboxylic acid: THC-COOH) has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine at concentrations >15 ng/mL is a strong indicator that the patient has used marijuana. The presence of THC-COOH in urine at concentrations >100 ng/mL indicates relatively recent use, probably within the past 7 days. Levels >500 ng/mL suggest chronic and recent use. Chronic use causes accumulation of the THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

**Reference Values:**
Negative
EMIT cutoff concentration: 50 ng/mL
Positives are reported with a quantitative GC/MS result.

**Clinical References:**
**Reference Values:**

<table>
<thead>
<tr>
<th>Drugs/Drug Classes</th>
<th>Screen Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>75 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>75 ng/mL</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Cocaine</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Methadone</td>
<td>40 ng/mL</td>
</tr>
<tr>
<td>Opiates</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30 ng/mL</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>15 ng/mL</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>75 ng/mL</td>
</tr>
</tbody>
</table>

Drugs/Drug classes reported as “Positive” are automatically reflexed to mass spectrometry confirmation/quantitation testing. An immunoassay unconfirmed positive screen result may be useful for medical purposes but does not meet forensic standards. For medical purposes only; not valid for forensic use.

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**DSSX 62723**

**Drug Screen, Prescription/OTC, Chain of Custody, Serum**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The test is not designed to screen for intermittent use of illicit drugs. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse/illicit drugs, some benzodiazepines, and most opiates. See Prescription and Over-the-Counter (OTC) Drug Screens Table 1 in Special Instructions. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to qualitatively identify drugs present in the specimen; quantification of identified drugs, when available, may be performed upon client request. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The drugs we know can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens Table 1 in Special Instructions. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If you wish to have a report interpreted, call Mayo Medical Laboratories and ask for a toxicology consultant. Mayo Medical Laboratories will only report reference ranges that we have determined to be clinically correlated. Other reference ranges are available from the literature, but since we have not validated them, we choose not to report them. We will gladly discuss them during a consultation and provide reference citations if requested. Each report will indicate the drugs detected.

**Reference Values:**
Drug detection


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**Drug Screen, Prescription/OTC, Chain of Custody, Urine**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The test is not designed to screen for intermittent use of illicit drugs. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse/illicit drugs, some benzodiazepines, and some opiates. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions.

**Useful For:** The qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to provide, when possible, the identification of all drugs present. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The drugs that can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. Positive results are definitive. Drugs of toxic significance that are not detected by this test include digoxin, lithium, many drugs of abuse/illicit drugs, some benzodiazepines, and some opiates. For these drugs, see Mayo Medical Laboratories' drug abuse surveys or drug screens or individual tests. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, request a Drug/Toxicology Lab consult (Mayo Clinic patients) or contact Mayo Laboratory Inquiry (Mayo Medical Laboratories clients).

**Reference Values:**


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**Drug Screen, Prescription/OTC, Serum**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs. The test is not designed to screen for intermittent use or illicit drugs. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse/illicit drugs, some benzodiazepines, and some opioids. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions.

**Useful For:** Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to qualitatively identify drugs present in
the specimen; quantification of identified drugs, when available, may be performed upon client request.

**Interpretation:** The drugs we know can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If you wish to have a report interpreted, call Mayo Medical Laboratories and ask for a toxicology consultant. Mayo Medical Laboratories will only report reference ranges that we have determined to be clinically correlated. Other reference ranges are available from the literature, but since we have not validated them, we choose not to report them. We will gladly discuss them during a consultation and provide reference citations if requested. Each report will indicate the drugs detected.

**Reference Values:**
Drug detection


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**Drug Screen, Prescription/OTC, Urine**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. The test is not designed to screen for intermittent use or illicit drugs. Drugs of toxic significance that are not detected by this test include: digoxin, lithium, and many drugs of abuse/illicit drugs, some benzodiazepines, and some opioids. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions.

**Useful For:** The qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to provide, when possible, the identification of all drugs present.

**Interpretation:** The drugs that can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. Drugs of toxic significance that are not detected by this test include: digoxin, lithium, many drugs of abuse/illicit drugs, some benzodiazepines, and some opiates. For these drugs, see Mayo Medical Laboratories’ drug abuse surveys or drug screens or individual tests. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, request a Drug/Toxicology Lab consult (Mayo Clinic patients) or contact Mayo Laboratory Inquiry (Mayo Medical Laboratories clients).

**Reference Values:**
Identification


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**Drugs of Abuse Screen 4, Chain of Custody, Meconium**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a higher incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, drug withdrawal) are increased. The disposition of drug in meconium is not well understood. The proposed
mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis.(2) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimen Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The limit of quantitation varies for each of these drug groups.  - Amphetamines: >100 ng/g  - Methamphetamines: >100 ng/g  - Cocaine and metabolite: >100 ng/g  - Opiates: >100 ng/g  - Tetrahydrocannabinol carboxylic acid: >20 ng/g

**Reference Values:**
Negative
Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**
- Amphetamines by ELISA: 100 ng/g
- Methamphetamine by ELISA: 100 ng/g
- Benzoylecgonine (cocaine metabolite) by ELISA: 100 ng/g
- Opiates by ELISA: 100 ng/g
- Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g

**Clinical References:**

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**DSM5X Drugs of Abuse Screen 5, Chain of Custody, Meconium**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress.(1) In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.
**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The limit of quantitation varies for each of these drug groups.
- Amphetamines: >100 ng/g
- Methamphetamines: >100 ng/g
- Cocaine and metabolite: >100 ng/g
- Opiates: >100 ng/g
- Tetrahydrocannabinol carboxylic acid: >20 ng/g
- Phencyclidine (PCP): >20 ng/g

**Reference Values:**

**Negative**
- Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**
- Amphetamines by ELISA: 100 ng/g
- Methamphetamine by ELISA: 100 ng/g
- Benzoylecgonine (cocaine metabolite) by ELISA: 100 ng/g
- Opiates by ELISA: 100 ng/g
- Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g
- Phencyclidine by ELISA: 20 ng/g

**Clinical References:**
Amphetamines: 500 ng/mL  
Barbiturates: 200 ng/mL  
Benzodiazepines: 200 ng/mL  
Cocaine (benzylecgonine-cocaine metabolite): 150 ng/mL  
Opiates: 300 ng/mL  
Phencyclidine: 25 ng/mL  
THC: 50 ng/mL  

Results of this test are confirmed and should be considered definitive.


Drugs of Abuse Screen, DAU8, Urine

Clinical Information: This test uses immunologic testing for drugs of abuse, by class, and screens for the presence of amphetamines, barbiturates, benzodiazepines, cocaine metabolite, opiates, phencyclidine, tetrahydrocannabinol, and ethanol. Positive immunologic results are confirmed by gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry with the exception of ethanol. Positive ethanol results are reported quantitatively directly from immunologic testing.

Useful For: Detecting drug abuse involving: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, tetrahydrocannabinol, and ethanol This test is intended to be used in a setting where the test results can be definitively to make a diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, DAUAM / Drugs of Abuse, Amphetamines GC-MS, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html Creatinine and specific gravity are measured as indicators of specimen dilution.

Reference Values:
Negative
The specific drug identified will be reported.
Cutoff concentrations
Amphetamines: 500 ng/mL  
Barbiturates: 200 ng/mL  
Benzodiazepines: 200 ng/mL  
Cocaine (benzylecgonine-cocaine metabolite): 150 ng/mL  
Opiates: 300 ng/mL  
Phencyclidine: 25 ng/mL  
THC: 50 ng/mL  
Ethanol: 10 mg/dL  

Results of this test are confirmed and should be considered definitive.


Drugs of Abuse Screen, DAU9, Urine

Clinical Information: This test uses immunologic testing for drugs by class and screens for the presence of amphetamines, barbiturates, benzodiazepines, cocaine metabolite, methadone, opiates, phencyclidine, and tetrahydrocannabinol in urine. Positive immunologic results are confirmed by gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry.
**Useful For:** Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, tetrahydrocannabinol, and methadone. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html. Creatinine and specific gravity are measured as indicators of specimen dilution.

**Reference Values:**

- **Negative**
  - The specific drug identified will be reported.

Enzyme-multiplied immunoassay technique cutoff concentrations:
- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 200 ng/mL
- Cocaine (benzoylcgonine-cocaine metabolite): 150 ng/mL
- Methadone: 300 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

Results of this test are confirmed and should be considered definitive.


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**Drugs of Abuse Screen, Meconium 4**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, drug withdrawal) are increased. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimen.

**Interpretation:** The limit of quantitation varies for each of these drug groups.
- Amphetamines: >100 ng/g
- Methamphetamines: >100 ng/g
- Cocaine and metabolite: >100 ng/g
- Opiates: >100 ng/g
- Tetrahydrocannabinol carboxylic acid: >20 ng/g

**Reference Values:**

- **Negative**
  - Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - Amphetamines by ELISA: 100 ng/g
  - Methamphetamine by ELISA: 100 ng/g
  - Benzoylcegonine (cocaine metabolite) by ELISA: 100 ng/g

Current as of July 8, 2016 11:28 am CDT
Opiates by ELISA: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g

**Clinical References:**

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**DASM5 60250**

**Drugs of Abuse Screen, Meconium 5**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens

**Interpretation:** The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g -Phencyclidine (PCP): >20 ng/g

**Reference Values:**
Negative
Cutoff concentrations
Amphetamines by ELISA: 100 ng/g
Methamphetamine by ELISA: 100 ng/g
Benzoylcegonine (cocaine metabolite) by ELISA: 100 ng/g
Opiates by ELISA: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g
Phencyclidine by ELISA: 20 ng/g

**Clinical References:**

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**DBMD 58125**

**Duchenne/Becker Muscular Dystrophy DMD Gene, Large Deletion and Duplication Analysis**

**Clinical Information:** Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder characterized initially by proximal muscle weakness beginning before age 5 years. Affected individuals typically have pseudohypertrophy of the calf muscles and exhibit toe-walking, waddling gait, and the...
Gower sign (climbing up the legs when rising from a seated position on the floor). Not only is skeletal muscle affected in DMD, but also the smooth muscle of the gastrointestinal tract and possibly bladder, as well as cardiac muscle. Initial symptoms are followed by dramatic progression of weakness leading to loss of ambulation by age 11 or 12. Death is often caused by cardiac failure or by respiratory failure before age 30, unless ventilator support is provided. The allelic Becker muscular dystrophy (BMD) has a similar presentation, although age of onset is later and the clinical course is much milder. Cardiac involvement can be the only sign and patients are often ambulatory into their thirties. DMD and BMD are caused by mutations in the DMD gene, which encodes for dystrophin. Approximately 50% to 65% of patients have intragenic deletions and approximately 5% to 10% have intragenic duplications. Less frequently, DMD and BMD result from nondeletion and nonduplication mutations, which are not detected by this assay. Approximately one-third of sporadic cases of DMD/BMD occur due to new mutations. In sporadic cases, it is possible for the mother of an affected individual to have germline mosaicism. This means that the germ cells may contain a mutation even if the mutation is not detected in peripheral blood. In cases of germline mosaicism, which occurs with a frequency of up to 15%, further offspring are at risk for inheriting a dystrophin mutation.

**Useful For:** Confirmation of a clinical diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) Distinguishing DMD from BMD in some cases, based on the type of deletion detected (allows for better prediction of prognosis) Determination of carrier status in family member at risk for DMD or BMD Prenatal diagnosis of DMD or BMD in at-risk pregnancies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Duck Feathers, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


Duck Meat IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

Duloxetine, Serum

Clinical Information: Duloxetine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class. It is effective in treating symptoms of depression, including physical pain associated with depression; other uses include therapy of neuropathic pain, fibromyalgia, and urinary stress incontinence. Duloxetine also inhibits serotonin uptake in human platelets, and may be associated with potentiation of bleeding. Duloxetine undergoes extensive hepatic biotransformation to numerous inactive metabolites. The drug is metabolized by CYP1A2 and CYP2D6, with moderate potential for drug interactions (duloxetine is both a substrate and a moderate inhibitor of CYP2D6). The mean elimination half-life is 12.5 hours with steady-state concentrations occurring in about 3 days. Specimens for therapeutic monitoring should be drawn immediately before the next scheduled dose (ie, trough). Duloxetine is not recommended for patients with hepatic impairment, substantial alcohol use, or chronic liver disease. Use in patients with renal disease significantly increases exposure to duloxetine due to decreased elimination. Patients with mild-to-moderate renal dysfunction should be monitored closely; use of duloxetine is not recommended in end-stage renal disease.

Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity Evaluating patient compliance

Interpretation: Therapeutic ranges are not well-established, but literature suggests that patients receiving duloxetine monotherapy for depression responded well when trough concentrations were 60 to 120 ng/mL. Higher levels may be tolerated by individual patients. The therapeutic relevance of this concentration range to other uses of duloxetine therapy is currently unknown.

Reference Values:
60-120 ng/mL

Eastern Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low-prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals, and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod, relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.

Useful For: Aiding the diagnosis of Eastern equine encephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity. Infections can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. Infection among males is primarily due to work conditions and sports activity taking place where the vector is present.

Reference Values:
IgG: <1:10
IgM: <1:10


ESYC
82721

Eastern Sycamore, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L   Interpretation
0              Negative
1              0.35-0.69 Equivocal
2              0.70-3.49 Positive
3              3.50-17.4 Positive
4              17.5-49.9 Strongly positive
5              50.0-99.9 Strongly positive
6              > or =100 Strongly positive Reference values apply to all ages.
FEAGR

Echinococcus Antibody (IgG), EIA with Reflex to Western Blot

**Interpretation:** Detection of serum antibodies to Echinococcus plays an important role in the diagnosis of hydatid disease, since infected individuals do not exhibit fecal shedding of Echinococcus eggs. Serum antibodies may remain detectable for years after cyst removal. Serologic crossreactivity between Echinococcus and Cysticercus may occur.

**Reference Values:**
Reference Range: Negative

ECHNO

Echinococcus Antibody, IgG, Serum

**Clinical Information:** Echinococcosis, also referred to as hydatidosis or hydatid disease, is one of the 17 neglected tropical diseases recognized by the World Health Organization, and affects over 1 million people worldwide. Echinococcus species are tapeworms or cestodes and 2 main species infect humans: Echinococcus granulosus and Echinococcus multilocularis. With respect to geographic distribution, E granulosus can be found worldwide, but more frequently in rural, grazing areas where dogs may feed on deceased, infected sheep or cattle. E multilocularis is largely localized to the northern hemisphere. The definitive hosts for E granulosus are dogs or other canids, while the definitive host for E multilocularis are foxes and, to a much lesser extent, canids. Echinococcus tapeworms reside in the small intestine of definitive hosts and release eggs that are passed in the feces and ingested by an intermediate host, typically sheep or cattle in the case of E granulosus or small rodents for E multilocularis. The eggs hatch in the small bowel, releasing an oncosphere, which penetrates the intestinal wall and migrates through the circulatory system to various organs where it will develop into a cyst that gradually enlarges producing protoscolcies and daughter cysts that fill the interior. The definitive host becomes infected following ingestion of these infectious cysts. Humans become accidentally infected following ingestion of Echinococcus eggs. In humans, E granulosus (cystic echinococcal disease) cysts typically develop in the lungs and liver and the infection may remain silent or latent for years (5-20 years) prior to cyst enlargement and symptom manifestation. Symptomatic manifestations include chest pain, hemoptysis and cough for pulmonary involvement and abdominal pain and biliary duct obstruction for liver infection. E multilocularis (alveolar echinococcal disease) infections manifest more rapidly than those of E granulosus, and manifests similar to a rapidly growing, destructive tumor resulting in abdominal pain and biliary obstruction. Rupture of cysts can produce fever, urticaria and anaphylactic shock. Diagnosis of echinococcal infections relies on characteristic finding by ultrasound or other imaging techniques and serologic findings. Fine needle aspirates of cystic fluid may be performed; however they carry the risk of cyst puncture and fluid leakage which may potentially lead to severe allergic reactions. Importantly, infected individuals do not shed eggs in stool.

**Useful For:** Detection of antibodies to Echinococcus species, including E multilocularis and E granulosus

**Interpretation:** Negative: the absence of antibodies to Echinococcus species suggests that the individual has not been exposed to this cestode. A single negative result should not be used to rule-out infection (see Cautions). Equivocal: consider repeat testing on a new serum sample in 1 to 2 weeks. Positive: results suggest infection with Echinococcus. False positive results may occur in settings of infection with other helminths, or in patients with chronic immune disorders. Results should be considered alongside other clinical findings and exposure history.

**Reference Values:**
Negative

**Clinical References:** 1. Higuita A, Brunetti E, McCloskey C: Cystic Echinococcosis. J Clin Micro
Echovirus Antibodies, CSF

**Reference Values:**

**REFERENCE RANGE:** < 1:1

**INTERPRETIVE CRITERIA:**

- < 1:1 Antibody Not Detected
- > or = 1:1 Antibody Detected

Diagnosis of infections of the central nervous system is accomplished by demonstrating the presence of intra-thecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

Echovirus Antibody Panel, CF (Serum)

**Reference Values:**

**Reference Range:** <1:8

- <1:8 Antibody not detected
- > or = 1:8 Antibody Detected

**INTERPRETIVE CRITERIA:**

- <1:8 Antibody not detected
- > or = 1:8 Antibody Detected

Single titers > or = 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

EGFR Gene, Mutation Analysis, 29 Mutation Panel, Tumor

**Clinical Information:** Lung cancer is the leading cause of cancer-related deaths in the world. Non-small cell lung cancer (NSCLC) represents 70% to 85% of all lung cancer diagnoses. Small molecular agents that target the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) protein are approved for the treatment of locally advanced or metastatic NSCLC as a second- or third-line regimen. Subsequently, randomized trials have suggested that targeted agents alone or combined with chemotherapy may be beneficial in maintenance and first-line settings. Because the combination of targeted therapy and standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from targeted therapies are desirable. EGFR is a growth factor receptor that is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression for many solid tumors. Targeted therapies directed to tumors harboring activating mutations within the EGFR tyrosine kinase domain (exons 18-21) have demonstrated some success in treating a subset of patients with NSCLC by preventing ATP-binding at the active site. Gefitinib and erlotinib have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to the traditional platinum-based doublet chemotherapy. These 2 drugs have also recently been shown to increase
progression-free and overall survival in patients who receive EGFR-tyrosine kinase inhibitor therapy as a first-line therapy for the treatment of NSCLC. Agents such as gefitinib and erlotinib, which prevent ATP binding to EGFR kinase, do not appear to have any meaningful inhibitor activity on tumors that demonstrate the presence of the specific drug-resistant EGFR mutation T790M. Therefore, current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I or small deletions within exon 19 and the absence of the drug-resistant mutation T790M. As a result, the mutation status of EGFR can be a useful marker by which patients are selected for EGFR-targeted therapy.

**Useful For:** Identifying non-small cell lung cancers that may respond to epidermal growth factor receptor-tyrosine kinase inhibitor therapies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### Egg White IgG

**FEGWH 57584**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Egg White IgG4

**FEWG4 57529**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**
<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

### Egg White, IgE

**EGG 82872**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsive for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Egg Yolk IgG

**Interpretation:** mcg/mL if IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Egg Yolk, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
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Eggplant, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Ehrlichia Antibody Panel, Serum

Clinical Information: See individual unit codes
**Useful For:** As an adjunct in the diagnosis of ehrlichiosis in seroepidemiological surveys of the prevalence of the infection in certain populations.

**Interpretation:** Serology for IgG may be negative during the acute phase of infection but a diagnostic titer usually appears by the third week after onset. A positive immunofluorescence assay (titer \( \geq 1:64 \)) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection.

**Reference Values:**

<1:64


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**EHRC**

**Ehrlichia chaffeensis (HME) Antibody, IgG, Serum**

**Clinical Information:** Ehrlichiosis is an emerging zoonotic infection caused by obligate intracellular, gram-negative rickettsia that infect leukocytes. Human monocytic ehrlichiosis (HME) is caused by Ehrlichia chaffeensis and is transmitted by the Lone Star tick, Amblyomma americanum. The deer is believed to be the animal reservoir and most cases of HME have been reported from the southeastern and south-central region of the United States. Infectious forms are ingested during tick bites and the organism enters the vascular system where it infects monocytes. It is sequestered in host-cell membrane-limited parasitophorous vacuoles known as morulae. These can be readily observed on Giemsa- or Wright-stained smears of peripheral blood from infected persons. Macrophages in organs of the reticuloendothelial system are also infected. Asexual reproduction occurs in WBCs and daughter cells are formed which are liberated upon cell rupture. Most cases of ehrlichiosis are probably subclinical or mild, but the infection can be severe and life-threatening; there is a 2% to 3% mortality rate. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Central nervous system involvement can result in seizures and coma. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings.

**Useful For:** As an adjunct in the diagnosis of ehrlichiosis and/or in seroepidemiological surveys of the prevalence of the infection in certain populations. Ehrlichiosis is sometimes diagnosed by observing the organisms in infected WBCs on Giemsa-stained thin blood films of smeared peripheral blood (morulae). Serology may be useful if the morulae are not seen or if the infection has cleared naturally or following treatment. Serology may also be useful in the follow-up of documented cases of ehrlichiosis or when coinfection with other tick-transmitted organisms is suspected. In selected cases, documentation of infection may be attempted by PCR methods.

**Interpretation:** A positive immunofluorescence assay (titer \( > or = 1:64 \)) suggests current or previous infection with Ehrlichia chaffeensis. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection.

**Reference Values:**

<1:64


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**FECHA**

**Ehrlichia chaffeensis Antibodies (IgG, IgM)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>&lt;1:64</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;1:20</td>
</tr>
</tbody>
</table>

Ehrlichia chaffeensis has been identified as the causative agent of Human Monocytic Ehrlichiosis.
Infected individuals produce specific antibodies to E. chaffeensis that can be detected by an immunofluorescent antibody (IFA) test. Single IgG IFA titers of 1:64 or greater indicate exposure to E. chaffeensis. A four-fold rise in IgG titers between acute and convalescent samples and/or the presence of IgM antibody against E. chaffeensis suggest recent or current infection.

**Clinical Information:** Ehrlichiosis and anaplasmosis are a group of emerging zoonotic tick-borne infections caused by Ehrlichia and Anaplasma species, respectively. These obligate intracellular, gram-negative rickettsial organisms infect leukocytes and cause a potentially serious febrile illness in humans. Human granulocytic anaplasmosis (HA) is caused by Anaplasma phagocytophilum, which is transmitted through the bite of an infected Ixodes sp. tick. The epidemiology of this infection in the United States is very much like that of Lyme disease (caused by Borrelia burgdorferi) and babesiosis (caused primarily by Babesia microti), which all have the same tick vector. HA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. Human monocytic ehrlichiosis (HE) is caused by Ehrlichia chaffeensis, which is transmitted by the Lone Star tick, Amblyomma americanum. Most cases of HE have been reported from the southeastern and south-central regions of the United States. Ehrlichia ewingii, the known cause of canine granulocytic ehrlichiosis, can occasionally cause an HE-like illness in humans. Clinical features and laboratory abnormalities are similar to those of Ehrlichia chaffeensis infection, and antibodies to Ehrlichia ewingii cross-react with current serologic assays for detection of antibodies to Ehrlichia chaffeensis. Most recently, Mayo Medical Laboratories detected a new species of Ehrlichia in patients with exposure to ticks in Wisconsin and Minnesota. This organism is most closely related to Ehrlichia muris and has therefore been referred to as the Ehrlichia muris-like agent or EMLA. The name E. muris eauclairensis has recently been proposed after the city in which the first case was described. Ehrlichia muris eauclairensis causes a similar disease to ehrlichiosis due to E. chaffeensis and E. ewingii, and may cause more severe disease in immunocompromised hosts. Most cases of anaplasmosis and ehrlichiosis are subclinical or mild, but infection can be severe and life-threatening in some individuals. Fever, fatigue, malaise, headache, and other "flu-like" symptoms, including myalgias, arthralgias, and nausea, occur most commonly. Central nervous system involvement can result in seizures and coma. Diagnosis may be difficult since the patient's clinical course is often mild and nonspecific. This symptom complex is easily confused with other illnesses such as influenza, or other tick-borne zoonoses such as Lyme disease, babesiosis, and Rocky Mountain spotted fever. Clues to the diagnosis of ehrlichiosis in an acutely febrile patient after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated serum aminotransferase levels. However, while these abnormal laboratory findings are frequently seen, they are not specific. Rarely, intra-granulocytic or monocytic morulae may be observed on peripheral blood smear, but this is not a reliable means of diagnosing cases of human ehrlichiosis or anaplasmosis. Definitive diagnosis is usually accomplished through PCR and serologic methods. Serologic testing is done primarily for confirmatory purposes, by demonstrating a 4-fold rise or fall in specific antibody titers to Ehrlichia species or Anaplasma antigens. There is not currently a commercially available specific serologic test for E. m. eauclairensis, but cross-reactivity with the other Ehrlichia species by serology may be detected. PCR techniques allow direct detection of pathogen-specific DNA from patients' whole blood and is the preferred method for detection during the acute phase of illness. The Mayo PCR assay is capable of detecting and differentiating A. phagocytophilum, E. chaffeensis, E. ewingii, and E. m. eauclairensis. It is important to note that concurrent infection with Anaplasma phagocytophilum, Borrelia burgdorferi, and Babesia microti is not uncommon as these organisms share the same Ixodes tick vector, and additional testing for these pathogens may be indicated.

**Useful For:** Evaluating patients suspected of acute anaplasmosis or ehrlichiosis

**Interpretation:** Positive results indicate presence of specific DNA from E. chaffeensis, E. ewingii, E. m. eauclairensis organism, or A. phagocytophilum and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens, but do not exclude the presence of these organisms or active or recent disease. Since DNA of Ehrlichia ewingii is indistinguishable from that of Ehrlichia canis by this rapid PCR assay, a positive result for Ehrlichia ewingii/canis indicates the presence of DNA from either of these 2 organisms.
Elastase, Pancreatic, Serum

**Clinical Information:** Serum Elastase, also called Pancreatopeptidase, is a protease present in pancreatic secretion with the unique ability to rapidly hydrolyze elastin. Elastin is a fibrillar protein found in connective tissue. Elastin forms the elastic fibers found mostly in lungs and skin. Elastase is able to hydrolyze denatured hemoglobin, casein, fibrin, albumin and denatured but not native collagen. Elastase has been implicated in the pathogenesis of pulmonary emphysema, atherosclerosis and in the vascular injury of acute pancreatic necrosis. Elastase activity is inhibited by protease inhibitors including a1-Anti-Trypsin, a1-anti-Chymotrypsin, anti-Thrombin III, a2-Macroglobulin and b1-anti-Collagenase. Patients with thyroid dysfunction have decreased Elastase activity. Serum pancreatic levels quantify EL 1 for the diagnosis or exclusion of an acute pancreatitis or an inflammatory episode of chronic pancreatitis or gallstone induced pancreatitis.

**Reference Values:**

**Adult Reference Ranges:**
- Normal pancreatic exocrine function: Less than 3.5 ng/mL

No pediatric reference ranges available for this test.

Elder, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class  IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


Electrolyte and Osmolality Panel, Feces
Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: - Normal daily dietary intake of electrolytes - Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure - Electrolyte transport into fecal water due to exogenous substances and rare toxins (e.g., cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolarity, and sodium is the major affecter of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars and can be characterized by the following: - Stool volume typically decreased by fasting - Fecal fluid usually has an elevated osmotic gap - Osmotic agents such as magnesium, sorbitol, or polyethylene glycol may be the cause through the intentional or inadvertent use of laxatives - Carbohydrate malabsorption due most commonly to lactose intolerance - Electrolyte malabsorption can be differentiated from other osmotic causes by a low stool pH (< 6) Secretory diarrhea is caused by disruption of epithelial electrolyte transport and can be characterized by the following: - Stool volume is usually unaffected by fasting - Fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (< 50 mOsm/kg) - Common causes include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia - Secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin should also be considered - Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms > 4 weeks)

Useful For: Workup of cases of chronic diarrhea Diagnosis of factitious diarrhea (where patient adds water to stool to simulate diarrhea)

Interpretation: Osmotic Gap: - Osmotic gap is calculated as 290 mOsm/kg - (2[Na]+2[K]). Typically, stool osmolarity is similar to serum since the gastrointestinal (GI) tract does not secrete water. (1) - An osmotic gap > 50 mOsm/kg is suggestive of an osmotic component contributing to the symptoms of diarrhea. (1-3) - Magnesium-induced diarrhea should be considered if the osmotic gap is > 75 mOsm/kg and is likely if the magnesium concentration is > 110 mg/dL. (1) - An osmotic gap < or = 50 mOsm/kg is suggestive of secretory causes of diarrhea. (1-3) - A highly negative osmotic gap or a fecal sodium concentration greater than plasma or serum suggests the possibility of either sodium phosphate or sodium sulfate ingestion by the patient. (4) Phosphorus: - Phosphorus elevation > 102 mg/dL is suggestive of phosphate-induced diarrhea. (4) Sodium: - Sodium is typically found at lower concentrations (mean 30 +/- 5 mmol/L) in patients with osmotic diarrhea caused by magnesium-containing laxatives, while typically at higher concentrations (mean 104 +/- 5 mmol/L) in patients known to be taking secretory laxatives. (5)
Osmolality: -Stool osmolality <220 mOsm/kg indicates dilution with a hypotonic fluid.(1) -Stool osmolality >330 mOsm/kg in the absence of increased serum osmolality indicates improper storage.(1) Sodium and Potassium: -High sodium and potassium in the absence of an osmotic gap indicate active electrolyte transport in the GI tract that might be induced by agents such as cholera toxin or hypersecretion of vasointestinal peptide.(1) Chloride: -Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea.(6) -Fecal chloride may be elevated (>35 mmol/L) in phenolphthalein- or phenolphthalein plus magnesium hydroxide-induced diarrhea.(3) -Fecal chloride may be low (<20 mmol/L) in sodium sulfate-induced diarrhea.(3)

Reference Values:
No established reference values


Electrolyte Panel, Serum

Clinical Information: See Individual Mayo Test IDs

Useful For: See Individual Mayo Test IDs

Interpretation: See Individual Mayo Test IDs

Reference Values:

SODIUM
- <1 year: not established
- > or =1 year: 135-145 mmol/L

POTASSIUM
- <1 year: not established
- > or =1 year: 3.6-5.2 mmol/L

CHLORIDE
- <1 year: not established
- 1-17 years: 102-112 mmol/L
- > or =18 years: 98-107 mmol/L

CREATININE
- Males
  - <1 year: not established
  - 1-2 years: 0.1â€“0.4 mg/dL
  - 3-4 years: 0.1-0.5 mg/dL
  - 5-9 years: 0.2â€“0.6 mg/dL
  - 10-11 years: 0.3â€“0.7 mg/dL
  - 12-13 years: 0.4â€“0.8 mg/dL
  - 14-15 years: 0.5â€“0.9 mg/dL
  - > or =16 years: 0.8â€“1.3 mg/dL
- Females

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 708
<1 year: not established
1-3 years: 0.1â€“0.4 mg/dL
4-5 years: 0.2â€“0.5 mg/dL
6-8 years: 0.3â€“0.6 mg/dL
9-15 years: 0.4â€“0.7 mg/dL
> or =16 years: 0.6â€“1.1 mg/dL

eGFR
>60 mL/min/1.73 m²
Note: eGFR results will not be calculated for patients <17 or >70 years old

BUN
Males
<1 year: not established
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL
Females
<12 months: not established
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL

BICARBONATE
Males
<1 year: not established
1-2 years: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L
Females
<1 year: not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

GLUCOSE
<1 year: not established
> or =1 year: 70-140 mg/dL

Clinical References: See Individual Mayo Test IDs

Electron Microscopy

Clinical Information: Crucial diagnostic information for the study of human disease may be provided by transmission and scanning electron microscopy. Often information of a confirmatory nature or of educational value to the clinician and pathologist can be obtained by this procedure. In recent years, the technology involved in electron microscopy has progressed to the point where methods have become standardized and the instrumentation routine. The electron microscope is a fundamental tool in medical diagnostic and cellular pathobiological investigations, because it is at this instrument's level of resolution that most structural correlations with function and metabolism are visible.

Useful For: Identifying tumor Diagnosing medical disorders such as storage diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and primary ciliary dyskinesia
**Interpretation:** The images and case histories are correlated and interpreted by a pathologist who is an expert in the field of the suspected diagnoses. Results will be provided by telephone. If requested, representative images showing diagnostic features will be sent.

**Reference Values:**
An interpretive report will be provided.


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**Electrophoresis, Protein, 24 Hour, Urine**

**Clinical Information:** Urine proteins can be grouped into 5 fractions by protein electrophoresis:
- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin
- Gamma-globulin

The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease.

**Useful For:** Monitoring patients with monoclonal gammopathies Urine protein electrophoresis alone is not considered an adequate screening for monoclonal gammopathies

**Interpretation:** A characteristic monoclonal band (M-spike) is often found in the urine of patients with multiple myeloma (MM). The initial identification of an M-spike or an area of restricted migration should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine that includes immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin heavy chain fragments as well as free light chains may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of >1 g/24 hours is consistent with a diagnosis of MM or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) which is predominantly albumin is consistent with amyloidosis (AL) or light chain deposition disease (LCDD). Because patients with AL and LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate "screen" for the disorder. MPSU / Monoclonal Protein Study, 24 Hour, Urine that includes immunofixation should be performed if the clinical suspicion is high.

**Reference Values:**

<table>
<thead>
<tr>
<th>PROTEIN, TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;167 mg/24 hours</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients <18 years of age.
Reference values have not been established for patients >83 years of age.

**ELECTROPHORESIS, PROTEIN**

If protein concentration is abnormal, the following fractions, if present, will be reported as a percent of the protein, total.
- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin
- Gamma-globulin

Reference value applies to 24-hour collection. Specimens collected for periods other than 24 hours will be reported in concentration units.

**Electrophoresis, Protein, Body Fluid**

**Clinical Information:** Body fluid proteins can be grouped into 5 fractions by protein electrophoresis (PEL): -Albumin -Alpha-1 Globulin -Alpha-2 Globulin -Beta Globulin -Gamma Globulin The concentration of these fractions and the electrophoretic pattern may identify abnormalities in the levels of the various fractions. Protein electrophoresis alone is not considered an adequate screening for body fluid or serum monoclonal gammopathies.

**Useful For:** Monitoring patient's body fluid proteins Aiding in the diagnosis of monoclonal gammopathies, when used in conjunction with immunofixation of the patient's serum Detecting oligoclonal banding in spinal fluid (the preferred test for detecting oligoclonal bands in spinal fluid is OLIG / Oligoclonal Banding, Serum and Spinal Fluid)

**Interpretation:** Monoclonal gammopathies: A characteristic monoclonal band (M-spike) is often found in the gamma-globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic body fluid protein electrophoresis pattern is suggestive of a possible monoclonal protein and should be followed by a MPSS / Monoclonal Protein Study, Serum using the patientâ€™s serum, which includes immunofixation to identify the immunoglobulin heavy chain and/or light chain.

**Reference Values:**
Not applicable


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**Electrophoresis, Protein, Random, Urine**

**Clinical Information:** Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma globulin The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease.

**Useful For:** Identifying patients with a monoclonal M-spike

**Interpretation:** A characteristic monoclonal band (M-spike) is often found in the urine of patients with multiple myeloma (MM). The initial identification of an M-spike or an area of restricted migration should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation electrophoresis to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin heavy chain fragments as well as free light chains may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of >1 g/24 hours is consistent with a diagnosis of MM or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) and light-chain deposition disease (LCDD). Because patients with AL and LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for the disorder. MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation electrophoresis, should be performed if the clinical suspicion is high.

**Reference Values:**
ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as a percent of the total protein.
- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 711
Gamma-globulin
No reference values apply to random urines.


PEL 80085

Electrophoresis, Protein, Serum

Clinical Information: Serum proteins can be grouped into 5 fractions by protein electrophoresis: - Albumin, which represents almost two-thirds of the total serum protein - Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein - Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin - Beta, composed primarily of transferrin and C3 - Gamma, composed primarily of immunoglobulins. The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

Useful For: Monitoring patients with monoclonal gammopathies. Diagnosis of monoclonal gammopathies, when used in conjunction with immunofixation. Protein electrophoresis alone is not considered an adequate screen for monoclonal gammopathies.

Interpretation: Monoclonal Gammapathies: - A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma-globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin heavy chain and/or light chain. - A monoclonal IgG or IgA >3 g/dL is consistent with multiple myeloma (MM). - A monoclonal IgG or IgA <3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. - A monoclonal IgM >3 g/dL is consistent with macroglobulinemia. - The initial identification of a serum M-spike >1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - The initial identification of an IgM, IgA, or IgG M-spike >4 g/dL, >5 g/dL, and >6 g/dL respectively, should be followed by VISCS / Viscosity, Serum. - After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is >0.5 g/dL is considered a significant change. - Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and should not be used to screen for the disorder. The MPSS / Monoclonal Protein Study, Serum, which includes immunofixation, and FLCP / Immunoglobulin Free Light Chains, Serum should be done to screen if the clinical suspicion is high. Other Abnormal PEL Findings: - A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. - A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. - A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult >40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin (A1AT) deficiency, hypoalbuminemia), the affected fraction is faint or absent. - An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-
Antitrypsin, Serum).

**Reference Values:**

**PROTEIN, TOTAL**

- \( \geq 1 \text{ year}: 6.3-7.9 \text{ g/dL} \)

Reference values have not been established for patients that are <12 months of age.

**PROTEIN ELECTROPHORESIS**

- Albumin: 3.4-4.7 g/dL
- Alpha-1-globulin: 0.1-0.3 g/dL
- Alpha-2-globulin: 0.6-1.0 g/dL
- Beta-globulin: 0.7-1.2 g/dL
- Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report.


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**Elm, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**FENC 90087**

**Encainide (Enkaidr), ODE and MODE**

**Reference Values:**

Encainide:
- Reference Range: 15 - 100 ng/mL

O-Demethylenencainide (ODE):
- Reference Range: 100 - 300 ng/mL

3-Methoxy-ODE (MODE):
- Reference Range: 60 - 300 ng/mL

10% of patients do not form therapeutic concentrations of the active metabolites, ODE and MODE. In these patients the recommended range for the encainide concentration is 300 - 1200 ng/mL.

**FENAP 58099**

**Encephalitis Antibody Panel (CSF)**

**Reference Values:**

Encephalitis Antibody Panel (CSF)

Lymphocytic Choriomeningitis (LCM) Virus Ab, IFA (CSF)
- Reference Range: IgG <1:1
  - IgM <1:1

Interpretive Criteria:
- <1:1: Antibody Not Detected
- 1:1: Antibody Detected

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. However, interpreting results is complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps.

This assay was developed and its performance characteristics determined by Focus Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

Measles (Rubeola) IgG and IgM Antibody Panel (CSF)
- Reference Range: IgG <1:64
  - IgM <1:1

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

This assay was developed and its performance characteristics determined by Focus Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical...
performance of the test.

Mumps Antibody Panel, IFA (CSF)

Reference Range:  
IgG  <1:8  
IgM  <1:1

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

This assay was developed and its performance characteristics determined by Focus Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

Varicella-Zoster Virus (VZV) Antibody (Total, IgM), ACIF/IFA, CSF

Reference Ranges:  
VZV Total AB  <1:2  
VZV IgM  <1:1

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

This assay was developed and its performance characteristics determined by Focus Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

West Nile Virus Antibodies (IgG, IgM), CSF

Reference Range:  
IgG  <1.30  
IgM  <0.90

Interpretive Criteria:

<table>
<thead>
<tr>
<th>IgG:</th>
<th>Antibody not detected</th>
<th>Equivocal</th>
<th>Antibody detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.30</td>
<td></td>
<td>1.30 – 1.49</td>
<td></td>
</tr>
<tr>
<td>&gt;=1.50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IgM:</th>
<th>Antibody not detected</th>
<th>Equivocal</th>
<th>Antibody detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.90</td>
<td></td>
<td>0.90 – 1.10</td>
<td></td>
</tr>
<tr>
<td>&gt;1.10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

West Nile Virus (WNV) IgM is usually detectable in CSF from WNV-infected patients with encephalitis or meningitis at the time of clinical presentation. Because IgM antibody does not readily cross the blood-brain barrier, IgM antibody in CSF strongly suggests acute central nervous system infection. WNV antibody results from CSF should be interpreted with caution. Possible complicating factors include low levels of antibody found in CSF, passive transfer of antibodies from blood and contamination via bloody spinal taps. Antibodies induced by other flavivirus infections (e.g. Dengue virus, St. Louis encephalitis virus) may show cross-reactivity with WNV.

Herpes Simplex Virus 1/2 (IgG) Type Specific Antibodies, CSF

Reference Range:  
< or = 1.00
**Interpretive Criteria:**

- **< or = 1.00**  
  Antibody not detected
- **>1.00**  
  Antibody detected

Detection of HSV type-specific IgG in CSF may indicate central nervous system (CNS) infection by that HSV type. However, interpretation of results may be complicated by a number of factors, including low antibody levels found in CSF, passive transfer of antibody across the blood-brain barrier, and serum contamination of CSF during CSF collection. PCR detection of type-specific HSV DNA in CSF is the preferred method for identifying HSV CNS infections.

**Herpes Simplex Virus 1/2 Antibody (IgM), IFA with Reflex to Titer, CSF**

**Reference Range:**  
Negative

The IFA procedure for measuring IgM antibodies to HSV 1 and HSV 2 detects both type-common and type-specific HSV antibodies. Thus, IgM reactivity to both HSV 1 and HSV 2 may represent cross-reactive HSV antibodies rather than exposure to both HSV 1 and HSV 2.

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

This test was developed and its characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.

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**ENCES**  
**61510**

**Encephalopathy, Autoimmune Evaluation, Serum**

**Clinical Information:** Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of 1 or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, LGI1 and CASPR2), ionotropic glutamate receptors (NMDA and AMPA), metabotropic GABA-B receptors; 2) enzymes, signaling molecules, and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (GAD65, CRMP-5, ANNA-1, and ANNA-2). Importantly, autoimmune encephalopathies are reversible. Misdiagnosed as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identifying patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidly progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebrospinal fluid (CSF), and 3) favorable response to a trial of immunotherapy. Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, neuronal voltage-gated potassium channel (VGKC)-complex antibodies were initially considered specific for autoimmune limbic
encephalitis or disorders of peripheral nerve hyperexcitability. However, more diverse presentations are now recognized, including rapidly progressive cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1, ANNA-1; collapsin response-mediator protein-5 neuronal, CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor, NMDA-R), and thymoma (CRMP-5 IgG). An individual patient's profile autoantibody may be informative for a specific cancer type. For example, detection of muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP 5 IgG in a patient presenting with encephalopathy suggests thymoma. When an associated tumor is found, its resection or ablation optimizes the neurological outcome. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative. Simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

**Useful For:** Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Inflammatory cerebral spinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

**Interpretation:** Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy. 1. Plasma membrane autoantibodies: voltage-gated potassium channel complex, N-Methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor; neuronal Ach receptor. These are all potential effectors of neurological dysfunction 2. Neuronal nuclear autoantibodies, type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3). 3. Neuronal or muscle cytoplasmic antibodies: amphiphysin, Purkinje cell antibodies (PCA-1) and PCA-2, CRMP-5, GA65, or striatinal.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Ab, Type 1 (ANNA-1) <1:240
- Antineuronal Nuclear Ab, Type 2 (ANNA-2) <1:240
- Antineuronal Nuclear Ab, Type 3 (ANNA-3) <1:240
- Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Ab, Type1 (PCA-1) <1:240
- Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2) <1:240
- Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr) <1:240
- Amphiphysin Antibody <1:240
- CRMP-5-IgG <1:240
WESTERN BLOT
Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody
< or =0.02 nmol/L

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L
N-Methyl-D-aspartate receptor (NMDA-R)
CBA: Negative
IFA: <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R)
CBA: Negative
IFA: <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
CBA: Negative
IFA: <1:120
NMO/AQP4-IgG
Negative

Clinical References:

ENCEC 61509
Encephalopathy, Autoimmune Evaluation, Spinal Fluid
Clinical Information: Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity,
spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of 1 or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, LGI1 and CASPR2), ionotropic glutamate receptors (NMDA and AMPA), metabotropic GABA-B receptors; 2) enzymes, signaling molecules and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (GAD65, CRMP-5, ANNA-1, and ANNA-2). Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identify patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidly progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebral spinal fluid (CSF), and 3) favorable response to a trial of immunotherapy. Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, neuronal voltage-gated potassium channel (VGKC)-complex antibodies were initially considered specific for autoimmune limbic encephalitis or disorders of peripheral nerve hyperexcitability. However, more diverse presentations are now recognized, including rapidly progressive cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1: ANNA-1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5 IgG). An individual patient’s profile autoantibody may be informative for a specific cancer type. For example, detection of muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP-5 IgG in a patient presenting with encephalopathy suggests thymoma. When an associated tumor is found, its resection or ablation optimizes the neurological outcome. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative. Simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

**Useful For:** Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Inflammatory cerebral spinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

**Interpretation:** Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient’s immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy. 1. Plasma membrane autoantibodies: These are all potential effectors of neurological dysfunction: neuronal voltage-gated potassium channel (VGKC)-complex, N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-aminobutyric acid (GABA-B) receptor; neuronal ACh receptor. 2. Neuronal nuclear autoantibodies: type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3) 3. Neuronal or muscle cytoplasmic antibodies: amphiphysin, Purkinje cell antibodies (PCA-1 and PCA-2), CRMP-5, GA65, or striational.

**Reference Values:**

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NEURONAL NUCLEAR ANTIBODIES
Antineuronal Nuclear Antibody-Type 1 (ANNA-1) <1:2
Antineuronal Nuclear Antibody-Type 2 (ANNA-2) <1:2
Antineuronal Nuclear Antibody-Type 3 (ANNA-3) <1:2
Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) <1:2

NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES
Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) <1:2
Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) <1:2
Purkinje Cell Cytoplasmic Antibody, Type TR (PCA-TR) <1:2
Amphiphysin Antibody <1:2
Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IGG) <1:2

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody Assay < or =0.02 nmol/L

AMPA-RECEPTOR ANTIBODY BY CBA
CBA: Negative
IFA: <1:2

GABA-B-RECEPTOR ANTIBODY BY CBA
CBA: Negative
IFA: <1:2

NMDA-RECEPTOR ANTIBODY BY CBA
CBA: Negative
IFA: <1:2

Neuronal Voltage-Gated Potassium Channel-Complex Autoantibody < or =0.02 nmol/L

WESTERN BLOT
Paraneoplastic Autoantibody, Western Blot Confirmation Negative
Collapsin Response-Mediator Protein-5-IGG (CRMP-5-IGG) Western Blot Negative
Amphiphysin Antibody Western Blot Negative

Neuromyelitis Optica (NMO)/Aquaporin-4-Igg Cell-Binding Assay Negative

Encephalopathy, Autoimmune Interpretation, Serum
Reference Values:
Only orderable as part of a profile. For more information see ENCES / Encephalopathy, Autoimmune Evaluation, Serum.

Encephalopathy, Autoimmune Interpretation, Spinal Fluid
Reference Values:
Only orderable as part of a profile. For more information see ENCEC / Encephalopathy, Autoimmune Evaluation, Spinal Fluid.

Endometrial Stromal Tumors (EST), 7p15 (JAZF1), 6p21.32 (PHF1), 17p13.3 (YWHAE) Rearrangement, FISH, Tissue
Clinical Information: Endometrial stromal tumors (EST) arise from the uterus and include the benign endometrial stromal nodule (ESN) and infiltrative endometrial stromal sarcoma (ESS). These tumors are characterized by a translocation that fuses JAZF1 at 7p15 to JJAZ1 at 17q21 or a variant 6;7 translocation involving JAZF1 and PHF1. Published literature employing FISH and reverse transcriptase PCR (RT-PCR) suggests rearrangement of JAZF1 occurs in approximately 76% of ESN and approximately 58% of ESS. JAZF1 is not generally considered to be involved in the genetic mechanism of the high-grade undifferentiated endometrial sarcoma (UES), although rarely some cases of UES are positive for JAZF1, which may reflect the presence of an ESS component. For PHF1 disruption, a study of 94 EST demonstrated the following: -PHF1/JAZF1 fusion in 4 primary ESS -PHF1/EPC1 fusion in 2 primary ESS and 1 extrauterine ESS -PHF1 rearrangement without a known partner in 6 primary or metastatic ESS and 1 extrauterine ESS JAZF1/JJAZ1, PHF1/JAZF1 and PHF1/EPC1 fusions were mutually exclusive in individual patients. No rearrangement of PHF1 was found in ESN, UES, or non-EST tumors in the differential diagnosis. These results indicate that PHF1 can rearrange with both known and unknown partners in addition to JAZF1 and is potentially specific for ESS. In high-grade ESS, a recurrent t(10;17)(q22;p13) resulting in fusion of YWHAE (also called 14-3-3epsilon at 17p13.3 with either FAM22A or FAM22B was identified. In contrast, JAZF1 rearrangements are typically observed in low-grade ESS. JAZF1 and YWHAE rearrangements are mutually exclusive and have distinct gene expression profiles. YWHAE rearrangement is potentially specific for high-grade ESS as no YWHAE disruption has been reported in other uterine or nonuterine mesenchymal tumors. The clinical utility of identifying JAZF1 rearrangement is mainly to address the differential diagnostic dilemma that occurs when ESS are present as metastatic lesions or exhibit variant morphology. In JAZF1-negative EST cases, reflex genetic analysis to identify PHF1 or YWHAE rearrangement increases the diagnostic sensitivity for EST. In addition, confirmation of YWHAE rearrangement may have prognostic implications as YWHAE defines a distinct, clinically more aggressive and histologically higher grade subgroup of ESS compared to those with JAZF1 rearrangements.

Useful For: Supporting the diagnosis of endometrial stromal tumors when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an endometrial stromal tumor of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Koontz J, Soreng AL, Nucci M, et al: Frequent fusion of the JAZF1 and

5362

Endomyocardial Biopsy

Clinical Information: Endomyocardial biopsies may be indicated to evaluate a variety of cardiac disorders. The procedure is performed using a device inserted through the jugular, subclavian, or femoral vein.

Useful For: Evaluation of: -Cardiac allograft rejection -Cardiomyopathies -Myocarditis -Idiopathic arrhythmias -Idiopathic chest pain -Anthracycline cardiotoxicity -Secondary heart disease (amyloidosis, sarcoidosis, hemochromatosis, storage diseases, and neoplastic diseases)

Interpretation: This request will be processed as a consultation. Appropriate stain(s) will be performed and a diagnostic interpretation provided.

Reference Values:
Abnormalities will be compared to reported reference values.


FEGAT

Endomysial (EMA) IgG antibody titer

Interpretation: Endomysial (EMA) antibody (IgG) screen: Positive findings of IgA class endomysial antibodies (IgA EMA) is consistent with dermatitis herpetiformis and/or celiac disease. If the disease is controlled by a gluten free diet, these antibodies will disappear. Repeat titrations for these IgA EMA can be used to monitor strict adherence to a gluten free diet. Negative results for IgA class endomysial antibodies are not consistent with a diagnosis of dermatitis herpetiformis or celiac disease. The sensitivity of this test on the average is about 70% in dermatitis herpetiformis and almost 100% in untreated Celiac Disease. Endomysial (EMA) antibody (IgG) titer: IgG-EMA is generally only significant in those individuals who are IgA deficient and thus cannot produce IgA-EMA.

Reference Values:
Negative: <1:2.5 titer
Positive: > or = 1:2.5 titer

EMA

Endomysial Antibodies (IgA), Serum

Clinical Information: Circulating IgA endomysial antibodies are present in 70% to 80% of patients
with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Diagnosis of dermatitis herpetiformis and celiac disease Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease Because of the high specificity of endomysial antibodies for celiac disease, the test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

**Interpretation:** The finding of IgA-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgA-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgA-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining or other factors; in this case, the results will be recorded as "indeterminate." In this setting, further testing with measurement of TTGA / Tissue Transglutaminase (tTG) Antibody, IgA, Serum and IGA / Immunoglobulin A (IgA), Serum levels are recommended.

**Reference Values:**
Report includes presence and titer of circulating IgA endomysial antibodies. Negative in normal individuals; also negative in dermatitis herpetiformis or celiac disease patients adhering to gluten-free diet. See Results of IF Testing* in Cutaneous Immunofluorescence Testing in Special Instructions.


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**English Plantain, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Entamoeba histolytica Antibody, Serum**

**Clinical Information:** Amebiasis is an infection by the protozoan parasite, Entamoeba histolytica. The infection is acquired by ingestion of cysts in fecally contaminated food or water; excystation and infection occur in the large intestine. After excystation, trophozoites attach to the intestinal wall and liberate extracellular enzymes that enable invasion of the mucosa and spread to other organs, especially the liver and lung where abscesses develop. Amebiasis (or amebic dysentery) can cause bloody diarrhea accompanied by fever and prostration. Leukocytes, WBCs, and RBCs are found in the stools. Liver abscess can develop several weeks to months later producing hepatomegaly and fever. Pathogenic (Entamoeba histolytica) and nonpathogenic (Entamoeba dispar) species of Entamoeba occur. Additionally, some of those infected with pathogenic strains are asymptomatic cyst carriers. Intestinal amebiasis should be diagnosed by detected Entamoeba histolytica in stool specimens.

**Useful For:** As an adjunct in the diagnosis of extraintestinal amebiasis, especially liver abscess

Serology may be particularly useful in supporting the diagnosis of amebic liver abscess in patients without a definite history of intestinal amebiasis and who have not spent substantial periods of time in endemic areas

**Interpretation:** A positive result suggests current or previous infection with Entamoeba histolytica. Since pathogenic and nonpathogenic species of Entamoeba cannot be differentiated microscopically, some authorities believe a positive serology indicates the presence of the pathogenic species (ie, Entamoeba histolytica).

**Reference Values:**

Expected values: negative


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**Entamoeba histolytica Antigen, EIA**

**Reference Values:**

E Histolytica Antigen: Not Detected
The Entamoeba histolytica antigen EIA test detects only the antigen of the pathogenic E. histolytica; the non-pathogenic E. dispar is not detected.

**Enteric Pathogens Culture, Stool**

**Clinical Information:** Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals) and these agents may result in similar symptoms. A thorough patient history covering symptoms, severity, duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician categorize the disease and ensure that any special requests are communicated to the laboratory.

**Useful For:** Determining whether a bacterial enteric pathogen is the cause of diarrhea. May be helpful in identifying the source of the infectious agent (eg, dairy products, poultry, water, or meat).

**Interpretation:** The growth of an enteric pathogen identifies the cause of diarrhea.

**Reference Values:**
No growth of pathogens.

**Clinical References:**

**Enterovirus Panel, CF, CSF**

**Reference Values:**
Reference Range and Interpretive Criteria for each component

(Coxsackie A Ab Panel, Coxsackie B Ab Panel, Echovirus Ab Panel)

REFERENCE RANGE: <1:1

INTERPRETIVE CRITERIA:
<1:1 Antibody Not Detected
> or = 1:1 Antibody Detected

Diagnosis of infections of the central nervous system is accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

**Enterovirus Panel, CF, Serum**

**Reference Values:**
ENTEROVIRUS PANEL, CF, SERUM
REFERENCE RANGE: <1:8

INTERPRETIVE CRITERIA for Coxsackie A, B and Echovirus:

<1:8 Antibody Not Detected
> or = 1:8 Antibody Detected

Single titers of > or = 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or
greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

**Enterovirus, Molecular Detection, PCR**

**Clinical Information:** Enteroviruses are positive-sense RNA viruses in the Picornaviridae family. These viruses were initially classified by serotype as polioviruses (3 types), echoviruses (31 types, including types 22 and 23, which are now classified as parechoviruses), coxsackievirus A (23 types), and coxsackievirus B (6 types). However, genomic studies have demonstrated that there is significant overlap in the biological characteristics of different serotypes and more recently isolated enteroviruses are now named with consecutive numbers (eg, EV68, EV69). The normal site of enterovirus replication is the gastrointestinal tract where the infection is typically subclinical. However, in a proportion of cases, the virus spreads to other organs, causing systemic manifestations, including mild respiratory disease (eg, the common cold); conjunctivitis; hand, foot, and mouth disease; aseptic meningitis; myocarditis; and acute flaccid paralysis. Collectively, enteroviruses are the most common cause of upper respiratory tract disease in children. In addition, the enteroviruses are the most common cause of central nervous system (CNS) disease; they account for almost all viruses recovered in culture from spinal fluid. Differentiation of enteroviruses from other viruses and bacteria that cause CNS disease is important for the appropriate medical management of these patients. Traditional cell culture methods require 6 days, on average, for enterovirus detection. In comparison, real-time PCR allows same-day detection. Detection of enterovirus nucleic acid by PCR is also the most sensitive diagnostic method for the diagnosis of CNS infection caused by these viruses.

**Useful For:** Aids in diagnosing enterovirus infections

**Interpretation:** A positive result indicates the presence of enterovirus RNA in the specimen.

**Reference Values:**

**Clinical References:**

Useful For: Aids in diagnosing enterovirus infections

Interpretation: A positive result indicates the presence of enterovirus RNA in the specimen.

Reference Values: Negative


**FECP**

Eosinophil Cationic Protein (ECP)

Reference Values:
2 â€“ 10 mcg/L

**EOSU**

Eosinophils, Urine

Clinical Information: Eosinophils are white blood cells that normally do not appear in urine. The presence of eosinophils in the urine is seen in acute interstitial nephritis, which is caused by an allergic reaction, typically to drugs.

Useful For: Investigation of possible acute interstitial nephritis

Interpretation: Greater than 5% eosinophils indicates acute interstitial nephritis; 1% to 5% eosinophils is indeterminant.

Reference Values: None seen


**FEPHD**

Ephedrine, Serum

Reference Values:
Reference Range: 35 - 80 ng/mL

**FENE**

Epicoccum nigrum IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

**EPUR**

Epicoccum purpurascens, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>1</td>
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<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Epidermal Nerve Fiber Density Consult

Clinical Information: Small fiber peripheral neuropathy is a common neurological complaint and a frequent source of morbidity in many patient populations. Direct investigation of small fiber involvement has been limited as most classical techniques such as electromyography (EMG), nerve conduction studies (NCS), and nerve biopsy, focus on large diameter nerve fibers and may be normal in patients with small fiber neuropathies. The advent of epidermal skin biopsies and PGP 9.5 immunohistochemistry allows the direct visualization and morphologic assessment of small sensory fibers innervating the skin.(1) Assessment of intraepidermal nerve fiber density (IENFD) has been used to reliably demonstrate pathologic abnormalities in small fiber neuropathy of various etiologies including diabetes, HIV, systemic lupus erythematosus, and neurosarcoidosis. Further, the technique has been validated, shown to have acceptable sensitivity and specificity, and is minimally invasive. The publication of normative data for commonly tested sites such as the distal and proximal legs and arms permits direct comparison of patients to age- and sex-matched controls facilitating localization and diagnosis.(2-4) Based on class 1 evidence and American Medical Association CPT code review process acceptance, IENFD measurements are now...
an accepted investigational method in the workup of polyneuropathy, including the characterization and
diagnosis of varieties of length-dependent small fiber polyneuropathies. IEFND measurements have been
incorporated in recent practice guidelines published by the American Academy of Neurology and the
European Federation of Neurological Science.(5,6)

**Useful For:** Investigation of polyneuropathies

**Interpretation:** The number of intraepidermally originating nerve fibers that cross the basement
membrane between the dermis and epidermis are counted in several sections.(2,5) The total linear length
of the epidermis is measured using standard morphometric techniques and a density of epidermal nerve
fibers (number of fibers/mm) is reported. This value is compared to previously published normative data.

**Reference Values:**
A consultative report will be provided.

**Clinical References:**
1. Lauria G, Lombardi R, Camozzi F, Devigili G: Skin biopsy for the diagnosis

**Epidermophyton floccosum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2
0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“

**Reference Values:**
<0.35 kU/L

**Epilepsy, Autoimmune Evaluation, Serum**

**Clinical Information:** Antiepileptic drugs (AEDs) are the mainstay of treatment for epilepsy, but
seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of
epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders,
including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive
manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis. Autoimmune
epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of
neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. The advent of more
sensitive and specific serological detection methods is increasingly revealing previously underappreciated
autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens
aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis.
Autoantibody specificities currently most informative for autoimmune epilepsies include voltage-gated
potassium channel-complex (VGKC-complex), glutamic acid decarboxylase-65 (GAD65), N
methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
receptors (AMPAR), and gamma aminobutyric acid type B receptor (GABABR) antibodies.
Autoantibodies recognizing onconeural proteins shared by neurons, glia or muscle (e.g., antineuronal nuclear antibody-type 1: ANNA 1, CRMP 5-IgG, N-type voltage-gated calcium channel and muscle AChR) also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient's autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds, justifies comprehensive evaluation of spinal fluid and serum for neural autoantibodies. Selective autoantibody testing is not advised because no single neural antibody is definitively associated with seizures, and markers of occult cancer may be missed. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

**Useful For:** Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of <2 years Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency), or multiple sclerosis -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without obvious cause, especially in a patient with past or family history of cancer -A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia. -Plasma membrane antibodies (N-methyl-D-aspartate: NMDA receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid: AMPA receptor; gamma-aminobutyric acid: GABA-B receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2: PCA-2, collapsin response-mediator protein-5 neuronal: CRMP-5-IgG, or glutamic acid decarboxylase: GAD65 antibody).

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**

- Antineuronal Nuclear Ab, Type 1 (ANNA-1) <1:240
- Antineuronal Nuclear Ab, Type 2 (ANNA-2) <1:240
- Antineuronal Nuclear Ab, Type 3 (ANNA-3) <1:240
- Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**

- Purkinje Cell Cytoplasmic Ab, Type1 (PCA-1) <1:240
- Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2) <1:240
- Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr) <1:240
- Amphiphysin Antibody <1:240
- CRMP-5-IgG <1:240

**WESTERN BLOT**

- Paraneoplastic Western Blot Negative
- CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody
< or =0.02 nmol/L

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L

N-Methyl-D-aspartate receptor (NMDA-R)
CBA: Negative
IFA: <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R)
CBA: Negative
IFA: <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
CBA: Negative
IFA: <1:120
NMO/AQP4-IgG
Negative

potassium channel-complex (VGKC-complex), glutamic acid decarboxylase-65 (GAD65), N methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPR) and gamma aminobutyric acid type B receptor (GABABR) antibodies. Autoantibodies recognizing onconeural proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody, type 1: ANNA 1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG; N-type calcium channel antibody, and acetylcholine receptor [muscle AChR] binding antibody) also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patientâ€™s autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of cerebral spinal fluid and serum for neural autoantibodies. Selective autoantibody testing is not advised because no single neural antibody is definitively associated with seizures, and markers of occult cancer may be missed. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

**Useful For:** Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of <2 years Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency) or â€œmultiple sclerosis” -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without -obvious cause, especially in a patient with past or family history of cancer

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune epilepsy: -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-amino butyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody). A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1)
  \(<1:2\)
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2)
  \(<1:2\)
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3)
  \(<1:2\)
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1)
  \(<1:2\)

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1)
  \(<1:2\)
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2)
  \(<1:2\)
- Purkinje Cell Cytoplasmic Antibody, Type TR (PCA-TR)
  \(<1:2\)
- Amphiphysin Antibody
  \(<1:2\)
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG)
  \(<1:2\)
ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody Assay
< or =0.02 nmol/L

AMPA-Receptor Antibody By CBA
CBA: Negative
IFA: <1:2

GABA-B-Receptor Antibody By CBA
CBA: Negative
IFA: <1:2

NMDA-Receptor Antibody By CBA
CBA: Negative
IFA: <1:2

Neuronal Voltage-Gated Potassium Channel-Complex Autoantibody
< or =0.02 nmol/L

WESTERN BLOT
Paraneoplastic Autoantibody, Western Blot Confirmation
Negative
Collapsin Response-Mediator Protein-5-IGG (CRMP-5-IGG) Western Blot
Negative
Amphiphysin Antibody Western Blot
Negative

Neuromyelitis Optica (NMO)/Aquaporin-4-Igg Cell-Binding Assay
Negative

Clinical References:

AEPSI 34259 Epilepsy, Autoimmune Interpretation, Serum
Reference Values:
Only orderable as part of a profile. For more information see EPIES / Epilepsy, Autoimmune Evaluation, Serum.

AEPCI 34258 Epilepsy, Autoimmune Interpretation, Spinal Fluid
Reference Values:
Only orderable as part of a profile. For more information see EPIEC / Epilepsy, Autoimmune Evaluation, Spinal Fluid.

EPIP1 81709 Epithelia Panel # 1
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from...
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
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<td>Strongly positive</td>
</tr>
<tr>
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<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Epstein-Barr Virus (EBV) Antibody Profile, Serum**

**Clinical Information:** Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be recognized, however, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test; eg, MONOS / Infectious Mononucleosis, Rapid Test, Serum), which usually appear within the first 3 weeks of illness, but then decline rapidly within a few weeks. The heterophile antibody, however, fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody-negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in a series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected but the heterophile antibody is not detected, an evaluation of the EBV-specific antibody profile (eg, EBV viral capsid antigen [VCA] IgM, EBV VCA IgG, and EBV nuclear antigen [EBNA]) may be useful. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection have been recognized for several years, including African-type Burkitt lymphoma and nasopharyngeal carcinoma. EBV infection may also cause lymphoproliferative syndromes, especially in patients who have undergone renal or bone marrow transplantation and in those who have AIDS.

**Useful For:** Diagnosing infectious mononucleosis when a mononucleosis screening procedure is negative and infectious mononucleosis or a complication of Epstein-Barr virus infection is suspected

**Interpretation:** The test has 3 components: viral capsid antigen (VCA) IgG, VCA IgM, and Epstein-Barr nuclear antigen (EBNA). Presence of VCA IgM antibodies indicates recent primary infection with Epstein-Barr virus (EBV). The presence of VCA IgG antibodies indicates infection sometime in the past. Antibodies to EBNA develop 6 to 8 weeks after primary infection and are detectable for life. Over 90% of the normal adult population has IgG class antibodies to VCA and EBNA. Few patients who have been infected with EBV will fail to develop antibodies to the EBNA (approximately 5%-10%). Possible Results VCA IgG VCA IgM EBNA IgG Interpretation - - - No previous exposure + +
- Recent infection + - + Past infection + - - See note* + + + Past infection *Results indicate infection with EBV at some time (VCA IgG positive). However, the time of the infection cannot be predicted (ie, recent or past) since antibodies to EBNA usually develop after primary infection (recent) or, alternatively, approximately 5% to 10% of patients with EBV never develop antibodies to EBNA (past).

**Reference Values:**

Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgM ANTIBODY  
Negative

Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgG ANTIBODY  
Negative

EPSTEIN-BARR NUCLEAR ANTIGEN (EBNA) ANTIBODIES  
Negative


80786  

**Epstein-Barr Virus (EBV) RNA Detection by In Situ Hybridization**

**Clinical Information:** Epstein-Barr virus (EBV) plays a pathogenic role in a variety of disease states, including infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma, B-cell lymphomas in patients with congenital or acquired immunodeficiency, and some cases of classical Hodgkin lymphoma.

**Useful For:** Detection of Epstein-Barr virus encoded RNA (EBER) in the diagnosis of EBV-associated conditions

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation/analysis is needed, please request test 70012 / Pathology Consultation along with this test.


EBVA  

8891  

**Epstein-Barr Virus (EBV), IgA, Serum**

**Clinical Information:** Infection with Epstein-Barr virus (EBV) usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infections, infectious mononucleosis is most common. Other disorders due to EBV infection have been recognized for several years, including African-type Burkitt lymphoma and nasopharyngeal carcinoma (NPC). The World Health Organization (WHO) classifies NPC as type 1 (keratinizing squamous cell carcinoma), type 2 (nonkeratinizing squamous cell carcinoma), and type 3 (undifferentiated carcinoma). EBV infection also may cause lymphoproliferative syndromes, especially in patients who have undergone renal or bone marrow transplantation and in those who have AIDS.

**Useful For:** The test is indicated for patients with malignant lesions of type 2 and 3 in whom nasopharyngeal carcinoma is suspected; eg, patients with metastases to the cervical lymph nodes from an...
Interpretation: Presence of IgA class antibody to the viral capsid antigen (VCA) of Epstein-Barr virus (EBV) indicates active replication of EBV. High levels of IgA class antibody to the VCA supports the clinical diagnosis of nasopharyngeal carcinoma (NPC). These antibodies are present in 84% of patients with type 2 NPC. IgA directed against VCA is positive for type 1 carcinoma in only 16% of cases. The specificity of the test is such that 82% to 91% of healthy blood donors and patients who do not have NPC have negative responses.

Reference Values:
<1:10

Reference Values:
Negative


Epstein-Barr Virus (EBV), Molecular Detection, PCR

Clinical Information: Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, Burkitt's lymphoma, and in Southern China, nasopharyngeal carcinoma. EBV-associated central nervous system (CNS) disease is most commonly associated with primary CNS lymphoma in patients with AIDS. In addition, CNS infection associated with the detection of EBV DNA can be seen in immunocompetent patients.

Useful For: Rapid qualitative detection of Epstein-Barr virus DNA in specimens for laboratory diagnosis of disease due to this virus

Interpretation: Detection of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid (CSF) supports the clinical diagnosis of central nervous system (CNS) disease due to the virus. EBV DNA is not detected in CSF from patients without CNS disease caused by this virus.

Reference Values:
Negative


Epstein-Barr Virus (EBV), Molecular Detection, PCR, Blood

Clinical Information: Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, Burkitt lymphoma, and in southern China, nasopharyngeal carcinoma. EBV-associated central nervous system (CNS) disease is most commonly associated with primary CNS lymphoma in patients with AIDS. In addition, CNS infection associated with the detection of EBV DNA can be detected in immunocompetent patients.

Useful For: Rapid qualitative detection of Epstein-Barr virus DNA in specimens for laboratory diagnosis of disease due to this virus

Interpretation: Detection of Epstein-Barr virus supports the clinical diagnosis of disease due to the virus.

Reference Values:
Negative

Epstein-Barr Virus (EBV), Molecular Detection, Quantitative PCR, Blood

Clinical Information: Primary infection with Epstein-Barr virus (EBV), a DNA-containing virus classified among the family Herpesviridae, may cause infectious mononucleosis resulting in a benign lymphoproliferative condition characterized by fever, fatigue, sore throat, and lymphadenopathy. Infection occurs early in life, and by 10 years of age, 70% to 90% of children have been infected with this virus. Usually, infection in children is asymptomatic or mild and may be associated with minor illnesses such as upper respiratory tract infection, pharyngitis, tonsillitis, bronchitis, and otitis media. The target cell for EBV infection is the B lymphocyte. Immunocompromised patients, lacking antibody to EBV, are at risk for acute EBV infection that may cause lymphoproliferative disorders in organ transplant recipients (posttransplant lymphoproliferative disorders [PTLD]) and AIDS-related lymphoma.(1) The incidence of PTLD ranges from 1% for renal transplant recipients, to as high as 9% for heart/lung transplants, and 12% for pancreas transplant patients. EBV DNA can be detected in the blood of patients with this viral infection; however, quantitative evaluation of EBV DNA has been shown to correlate highly with the subsequent (3-4 months) development of PTLD in susceptible patients.(2) Organ transplant recipients seronegative (risk for primary EBV infection) for EBV (frequently children) who receive anti-lymphocyte globulin for induction immunosuppression and OKT-3 treatment for early rejection are at highest risk for developing PTLD compared to immunologically normal individuals with prior infection with this virus.(4,5)

Useful For: A prospective and diagnostic marker for the development of posttransplant lymphoproliferative disorders (PTLD), especially in Epstein-Barr virus (EBV)-seronegative organ transplant recipients who receive anti-lymphocyte globulin for induction immunosuppression and OKT-3 treatment for early rejection

Interpretation: Increasing copy levels of Epstein-Barr virus (EBV) DNA in serial specimens may indicate possible posttransplant lymphoproliferative disorders (PTLD). Positive results are quantitated in copies/mL. Reportable range is 2,000 to 200,000,000 copies/mL. Specimens with results <5,000 copies EBV DNA/mL include a disclaimer that states: “Results may not be reproducible due to low copy number.” Blood specimens of normal blood donors for EBV infection usually have low or undetectable levels of viral DNA.

Reference Values: None detected


**Erythrocytosis Evaluation**

**Clinical Information:** Erythrocytosis (increased red blood cell mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (Epo) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be present. A less common cause of secondary polycythemia is the presence of a high-oxygen-affinity hemoglobin. A subset of hemoglobins with increased oxygen (O2) affinity result in clinically evident erythrocytosis caused by decreased O2 unloading at the tissue level. The most common symptoms are headache, dizziness, tinnitus, and memory loss. The affected individuals are plethoric, but not cyanotic. Patients with a high-oxygen-affinity hemoglobin may present with an increased erythrocyte count, hemoglobin concentration, and hematocrit, but normal leukocyte and platelet counts. The p50 and 2,3-bisphosphoglycerate (2,3-BPG, also known as 2,3-DPG) values are low. Changes to the amino acid sequence of the hemoglobin molecule may distort the molecular structure, affecting O2 transport and the binding of 2,3-BPG. 2,3-BPG is critical to O2 transport of erythrocytes because it regulates the O2 affinity of hemoglobin. A decrease in the 2,3-BPG concentration within erythrocytes results in greater O2 affinity of hemoglobin and reduction in O2 delivery to tissues. A few cases of erythrocytosis have been described as being due to a reduction in 2,3-BPG formation. This is most commonly due to mutations in the converting enzyme, bisphosphoglycerate mutase (BPGM). Mutations in the genes EPOR, EPAS1(HIF2A), EGLN1(PHD2), and VHL also cause hereditary erythrocytosis and a subset are associated with subsequent pheochromocytoma and paragangliomas. The prevalence of these mutations is unknown, but they appear less prevalent than mutations that cause high-oxygen-affinity hemoglobin variants, and much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful. Initial JAK2 V617F mutation testing and serum Epo levels are important with p50 results further stratifying JAK2-negative cases.

**Useful For:** Definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell mass, elevated red blood cell count, hemoglobin, or hematocrit

**Interpretation:** The evaluation includes testing for a hemoglobinopathy and oxygen (O2) affinity of the hemoglobin molecule. An increase in O2 affinity is demonstrated by a shift to the left in the O2 dissociation curve (decreased p50 result). A hematopathologist expert in these disorders will evaluate the case, appropriate tests are performed, and an interpretive report is issued.

**Reference Values:**
Definitive results and an interpretive report will be provided.

**Erythropoietin (EPO), Serum**

**Clinical Information:** Erythropoietin (EPO), a large (193 amino acid residue) glycoprotein hormone secreted by the kidney, regulates RBC production. Normally, EPO levels vary inversely with hematocrit. Hypoxia stimulates EPO release, which, in turn, stimulates bone marrow erythrocyte production. High blood levels of RBC, hemoglobin, hematocrit, or oxygen suppress the release of EPO. Primary polycythemia (polycythemia vera) is a neoplastic (clonal) blood disorder characterized by autonomous production of hematopoietic cells. Increased erythrocytes result in compensatory suppression of EPO levels. Findings consistent with polycythemia vera include hemoglobin >18.5 gm/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia (dysesthesia and erythema involving the distal extremities). Secondary polycythemias may either be due to an appropriate or an inappropriate increase in red cell mass. Appropriate secondary polycythemias (eg, high-altitude living and pulmonary disease) are characterized by hypoxia and a compensatory increase in red cell mass. EPO production is increased in an attempt to increase the delivery of oxygen by increasing the number of oxygen-carrying RBCs. Some tumors secrete EPO or EPO-like proteins; examples include tumors of the kidney, liver, lung, and brain. Such increases result in inappropriate secondary polycythemias. Abnormal EPO levels also may be seen in renal failure. The majority of EPO production is in the kidneys. Therefore, chronic renal failure may result in decreased renal EPO production and, subsequently, anemia. In addition to the kidneys, the liver also produces a small amount of EPO. Thus, anephric patients have a residual amount of EPO produced by the liver. Chronic renal failure patients, as well as patients with anemia due to a variety of other causes including chemotherapy, HIV/AIDS, and some hematologic disorders may be candidates for treatment with recombinant human EPO. Recombinant EPO compounds used to treat anemia include epoetin alpha and darbepoetin. Epoetin alpha is a 165 amino acid glycoprotein produced in mammalian cells and has an identical amino acid sequence to natural human EPO. It has 3 oligosaccharide chains and a molecular mass of 30.4 kDa. Darbepoetin alpha is a 165 amino acid glycoprotein that is also produced in mammalian cells. It has 2 additional N-linked oligosaccharide chains and a molecular mass of 37 kDa. There are no specific assays for measuring recombinant EPO compounds. Drug levels can only be roughly estimated from the cross reactivity of the compounds in EPO assays. According to in-house studies, epoetin and darbepoetin show approximately 58% and 36% cross-reactivity, respectively, in the EPO assay.

**Useful For:** An aid in distinguishing between primary and secondary polycythemia Differentiating between appropriate secondary polycythemia (eg, high-altitude living, pulmonary disease, tobacco use) and inappropriate secondary polycythemia (eg, tumors) Identifying candidates for erythropoietin (EPO) replacement therapy (eg, chronic renal failure) Evaluating patients undergoing EPO replacement therapy who demonstrate an inadequate hematopoietic response

**Interpretation:** In the appropriate clinical setting (eg, confirmed elevation of hemoglobin >18.5 gm/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia), polycythemia vera is unlikely when erythropoietin (EPO) levels are elevated and polycythemia vera is likely when EPO levels are suppressed. EPO levels are also increased in patients with anemia of bone marrow failure, iron deficiency, or thalassemia. Patients, who have either a poor or no erythropoietic response to EPO therapy, but high-normal or high EPO levels, may have additional, unrecognized cause(s) for their anemia. If no contributing factors can be identified after adequate further study, the possibility that the patient may have developed EPO-antibodies should be considered. This can be a serious clinical situation that can result in red cell aplasia, and should prompt expeditious referral to hematologists or immunologists skilled in diagnosing and treating this disorder.

**Reference Values:**
2.6-18.5 mIU/mL

**Erythropoietin Receptor (EPOR) Gene, Exon 8 Sequencing**

**Clinical Information:** Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Useful For:** Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Interpretation:** Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Clinical References:**

---

**Estradiol Free, Serum (includes Estradiol and SHBG)**

**Reference Values:**
Free Estradiol, Percent
Reference Ranges (%)

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>1.7 - 5.4</td>
</tr>
<tr>
<td>Adult Females</td>
<td>1.6 - 3.6</td>
</tr>
</tbody>
</table>

Free Estradiol, Serum
Reference Ranges (pg/mL)

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Adult Males</td>
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<tr>
<td>Adult Females</td>
<td>0.6 - 7.1</td>
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</table>

Sex Hormone Binding Globulin (SHBG), Serum
Reference Ranges (nmol/L)

<table>
<thead>
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</tr>
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<tbody>
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<td>60 - 252</td>
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<tr>
<td>Prepubertal (24m - 8y)</td>
<td>72 - 220</td>
</tr>
<tr>
<td>Pubertal</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>16 - 100</td>
</tr>
<tr>
<td>Females</td>
<td>36 - 125</td>
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<tr>
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<td>20 - 60</td>
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<td>Adult Females</td>
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<tr>
<td>Premenopausal</td>
<td>40 - 120</td>
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<tr>
<td>Postmenopausal</td>
<td>28 - 112</td>
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Estradiol, Serum
Reference Ranges (pg/mL)

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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<tbody>
<tr>
<td>Newborn</td>
<td></td>
</tr>
<tr>
<td>Levels are markedly elevated at birth and fall rapidly during the first week to prepubertal values of &lt;15</td>
<td></td>
</tr>
<tr>
<td>Males &lt;6m</td>
<td>Levels increase to 10 - 32 between 30 and 60 days, then decline to prepubertal levels of &lt;15 by six months.</td>
</tr>
<tr>
<td>Females &lt;1y</td>
<td>Levels increase to 5.0 - 50 between 30 and 60 days, then decline to prepubertal levels of &lt;15 during the first year.</td>
</tr>
</tbody>
</table>
Estrogens are responsible for the development and maintenance of female sex organs and female secondary sex characteristics. In conjunction with progesterone, they participate in regulation of the menstrual cycle, breast and uterine growth, and in the maintenance of pregnancy. Estrogens affect calcium homeostasis and have a beneficial effect on bone mass. They decrease bone resorption and, in prepubertal girls, estrogen accelerates linear bone growth. Long-term estrogen depletion is associated with loss of bone mineral content, an increase in stress fractures, and postmenopausal osteoporosis. The 3 most biologically active estrogens in order of potency are estrone (E1), estradiol (E2), and estriol (E3). Estrogens are produced primarily in the ovary (follicle, corpus luteum), but small quantities are also formed in the testes and in the adrenal cortex. During pregnancy, estrogens are mainly formed in the placenta. About 98% of estradiol is bound to transport proteins (sex hormone-binding globulin: SHBG) and albumin. Estrogen secretion is biphasic during the menstrual cycle. The determination of estradiol is utilized clinically in the elucidation of fertility disorders in the hypothalamus-pituitary-gonad axis, gynecomastia, estrogen-producing ovarian and testicular tumors, and in hyperplasia of the adrenal cortex. Additional clinical indications are the monitoring of fertility therapy and determining the time of ovulation within the framework of in vitro fertilization (IVF). The laboratory plays an important role in the process of ovulation induction. The principle involves administration of gonadotropins to stimulate follicular growth, followed by human chorionic gonadotropin (hCG) to stimulate ovulation follicular maturation. Clinical, laboratory, and ultrasound monitoring of the treatment cycle is necessary to identify the dose and length of therapy, determine when or whether to administer hCG, and obtain an adequate ovulatory response while avoiding hyperstimulation.

**Useful For:** Rapid assessment of ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) Establishing time of ovulation and optimal time for conception For other clinical indications, order EEST / Estradiol, Serum.

**Interpretation:** Optimal time for conception is within 48 to 72 hours following the midcycle estradiol peak. Serial specimens must be drawn over several days to evaluate baseline and peak estradiol levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization (IVF) studies, low levels before stimulation are critical, as higher values often are associated with poor stimulation cycles. Before final human chorionic gonadotropin (hCG) stimulation at mid-IVF cycle, estradiol concentrations above 2,000 to 3,000 pg/mL are considered by some IVF specialists to be indicative of an increased likelihood of ovarian hyperstimulation and it may be advisable to consider withholding further hCG stimulation. Estradiol (E2) concentrations <200 pg/mL following midcycle stimulation (hCG or follicle-stimulating hormone: FSH) are associated with very low pregnancy success rates. E2 concentrations change during the menstrual cycle, as follows: <50 pg/mL before mid-follicular phase -250 to 500 pg/mL midcycle peak as the follicle matures -Abrupt decrease after ovulation -125 pg/mL peak during the luteal phase Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women and luteinizing hormone and FSH should be within the normal range.

**Reference Values:**
Males: 10-40 pg/mL
Females
  Premenopausal: 15-350 pg/mL*
  Postmenopausal: <10 pg/mL
  *Estradiol concentrations vary widely throughout the menstrual cycle

The limit of quantitation for estradiol measured by immunoassay is 25 pg/mL. Mass spectrometry is the preferred method for measurement of low serum estradiol concentrations in children, males and postmenopausal females (EEST / Estradiol, Serum).


Estradiol, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in oocytes and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and post-menopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone (LH)/follicle stimulating hormone (FSH) surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. See Steroid Pathways in Special Instructions.

Useful For: All applications that require moderately sensitive measurement of estradiol: -Evaluation of hypogonadism and oligo-amenorrhea in females -Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) -In conjunction with luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women -Evaluation of feminization, including gynecomastia, in males -Diagnosis of estrogen-producing neoplasms in males, and, to a lesser degree, females -As part of the diagnosis and work-up of precocious and delayed puberty in females, and, to a lesser degree, males -As part of the diagnosis and work-up of suspected disorders of sex steroid metabolism, eg, aromatase deficiency and 17 alpha-hydroxylase deficiency -As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men -Monitoring low-dose female hormone replacement therapy in post-menopausal women -Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)
**Interpretation:** Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmun e polyglandular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately "normal," a diagnosis of hypogonadotrophic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further work-up is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging. Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone [E1] levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. E2 levels change during the menstrual cycle, as follows: -Post-menstrual, levels may be as low as 15 pg/mL. -Levels then rise during the follicular phase to a pre-ovulatory peak, typically in the 300+ pg/mL range. -Levels fall in the luteal phase. -Menses typically occur when E2 levels are in the 50 to 100 pg/mL range. E2 analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be drawn over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation, are critical, as higher levels are often associated with poor stimulation cycles. Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically <5 pg/mL in these patients. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization. -Obesity with increased tissue production of E1. -Decreased E1 and E2 clearance in liver disease. -Estrogen producing tumors. -Estrogen ingestion. Normal male E1 and E2 levels also may be associated with feminization or gynecomastia, if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the work-up for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels <10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo-precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallmann syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are
usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. See Steroid Pathways in Special Instructions.

**Reference Values:**

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<td>Undetectable-13 pg/mL</td>
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<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>Undetectable-26 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1 years</td>
<td>Undetectable-38 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-40 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.</td>
</tr>
</tbody>
</table>

**Females**

<table>
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<th>Tanner Stages#</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
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<tbody>
<tr>
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<td>Undetectable-20 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>Undetectable-24 pg/mL</td>
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<td>Stage III</td>
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<td>Stage IV</td>
<td>12.3 years</td>
<td>15-85 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>14.5 years</td>
<td>15-350 pg/mL ** #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. **The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data, and on our data for young adults. ADULTS Males: 10-40 pg/mL Females Premenopausal: 15-350 pg/mL ** Postmenopausal: **E2 levels vary widely through the menstrual cycle. Conversion factor E2: pg/mL x 3.676=pmol/L (molecular weight=272)</td>
</tr>
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</table>
Estriol, Unconjugated, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important in many other nongender-specific functions in men and women. These include growth, nervous system maturation, bone metabolism, and endothelial responsiveness. There are 3 major biologically active estrogens in humans: estrone (E1), estradiol (E2), and estriol (E3). Like all members of the steroid hormone family, they diffuse into cells and bind to specific nuclear receptors, which in turn alter gene transcription in a tissue specific manner. E2 is the most potent natural human estrogen, closely followed by E1, while E3 possess only 20% of E2's affinity for the estrogen receptor. In men and nonpregnant women, E1 and E2 are formed from the androgenic steroids androstenedione and testosterone, respectively. E3 is derived largely through conversion of E2, and to a lesser degree from 16a-metabolites of E1. E2 and E1 can also be converted into each other, and both can be inactivated via hydroxylation and conjugation. During pregnancy E3 becomes the dominant estrogen. The fetal adrenal gland secretes dehydroepiandrosterone-sulfate (DHEAS), which is converted to E3 in the placenta and diffuses into the maternal circulation. The half-life of unconjugated E3 (uE3) in the maternal blood system is 20 to 30 minutes, since the maternal liver quickly conjugates E3 to make it more water soluble for urinary excretion. E3 levels increase throughout the course of pregnancy, peaking at term. Measurement of serum E2 and E1 levels is an integral part of assessment of reproductive function in females, and also has applications in both men and women in osteoporosis risk assessment and monitoring of female hormone replacement therapy. By contrast, with the exception of epidemiological studies assessing breast cancer risk and other scientific studies, the main value of E3 measurements is in the diagnosis of maternal-fetal diseases. In those settings, measurement of serum uE3 levels plays a major role. Decreased 2nd trimester uE3 has been shown to be a marker for Down and trisomy-18 syndromes. It also is low in cases of gross neural tube defects such as anencephaly. Based on these observations, uE3 has become a part of multiple marker prenatal biochemical screening, together with alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and inhibin-A measurements (QUAD / Quad Screen (Second Trimester) Maternal, Serum). Low levels of uE3 also have been associated with pregnancy loss, Smith-Lemli-Opitz syndrome (defect in cholesterol biosynthesis), X-linked ichthyosis and contiguous gene syndrome (placental sulfatase deficiency disorders), aromatase deficiency, and primary or secondary fetal adrenal insufficiency. High levels of uE3, or sudden increases in maternal uE3 levels, are a marker of pending labor. The rise occurs approximately 4 weeks before onset of labor. Since uE3 has been shown to be more accurate than clinical assessment in predicting labor onset, there is increasing interest in its use in assessment of pre-term labor risk. High maternal serum uE3 levels may also be occasionally observed in various forms of congenital adrenal hyperplasia.

Useful For: A part of the QUAD / Quad Screen (Second Trimester) Maternal, Serum in biochemical second trimester or cross-trimester screening for Down syndrome and trisomy 18 syndrome A marker of fetal demise An element in the prenatal diagnosis of disorders of fetal steroid metabolism, including Smith-Lemli-Opitz syndrome, X-linked ichthyosis and contiguous gene syndrome (placental sulfatase deficiency disorders), aromatase deficiency, primary or secondary fetal adrenal insufficiency, and various forms of congenital adrenal hyperplasia The assessment of preterm labor risk Epidemiological studies of breast cancer risk in conjunction with measurement of estrone, estradiol, and various metabolites Assessing estrogen metabolism, estrogen and estrogen-like medications, and other endogenous or exogenous factors impacting on estrogen metabolism in the context of other basic scientific and clinical studies

Interpretation: In the context of the quad test, the measured unconjugated E3 (uE3) value forms part of a complex, multivariate risk calculation formula, using maternal age, gestational stage, and other demographic information, in addition to the results of the other tested markers, for Down syndrome, trisomy 18 syndrome, and neural tube defect risk calculations. A serum uE3 <0.3 multiples of the gestational age...
median in women who otherwise screen negative in the quad test, indicates the possibility of fetal demise, Smith-Lemli-Opitz syndrome, X-linked ichthyosis or contiguous gene syndrome, aromatase deficiency, or primary or secondary (including maternal corticosteroid therapy) fetal adrenal insufficiency. An elevated serum or uE3 >3 multiples of the gestational age mean, or with an absolute value of >2.1 ng/mL, can be an indication of pending labor or fetal congenital adrenal hyperplasia. In the context of assessment of a patient deemed at risk of preterm labor, a single serum or uE3 measurement within the above cutoffs, has a negative predictive value of labor onset (ie, labor unlikely within the next 4 weeks) of 98% in low-risk populations and of 96% in high-risk populations. Measurements of serum uE3 performed in the context of epidemiological or other basic or clinical scientific studies need to be interpreted in the context of those studies. No overall guidelines can be given.

**Reference Values:**
Males: <0.07 ng/mL  
Females: <0.08 ng/mL

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**89213**

**Estrogen/Progesterone Receptor, Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** The steroid hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), are commonly used in the management of women with breast cancer. ER and PR status provide an indication of prognosis and of the potential to benefit from hormonal therapy. Generally, ER/PR-positive tumors are more likely to respond to endocrine therapy and have a better prognosis, stage-for-stage, than receptor-negative tumors.

**Useful For:** The test is most frequently used in breast carcinomas when decisions on hormonal therapy must be made. While the test can be performed on any formalin-fixed, paraffin-embedded tissue, it is infrequently used for non-breast cancer specimens.

**Interpretation:** Immunoperoxidase-stained slides are examined microscopically by the consulting anatomic pathologist and interpreted as negative (<1% reactive cells), focally positive (1%-10% reactive cells), or positive (>10% reactive cells).

**Reference Values:**
Negative: <1% reactive cells  
Focal positive: 1-10% reactive cells  
Positive: >10% reactive cells


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**ESTF 84230**

**Estrogens, Estrone (E1) and Estradiol (E2), Fractionated, Serum**

**Clinical Information:** Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, non-gender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in...
premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then gradually increase again until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment.

**Useful For:** This test allows the simultaneous high-sensitivity determination of serum estrone and estradiol levels. It is useful in situations requiring either higher sensitivity estradiol measurement, or estrone measurement, or both. This includes the following: -As part of the diagnosis and work-up of precocious and delayed puberty in females, and, to a lesser degree, males -As part of the diagnosis and work-up of suspected disorders of sex steroid metabolism, eg, aromatase deficiency and 17 alpha-hydroxylase deficiency -As an adjunct to clinical assessment, imaging studies, and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men -Monitoring low-dose female hormone replacement therapy in postmenopausal women -Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy) Useful in all applications that require moderately sensitive measurement of estradiol including: -Evaluation of hypogonadism and oligo-amenorrhea in females -Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) In conjunction with luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women Evaluation of feminization, including gynecomastia, in males Diagnosis of estrogen-producing neoplasms in males, and, to a lesser degree, females

**Interpretation:** Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmune polyglandular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately “normal,” a diagnosis of hypogonadotrophic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further work-up is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging. Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone [E1] levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. E2 analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be drawn over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation are critical, as higher values often are associated with poor stimulation cycles. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels
should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically <5 pg/mL. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal male E1 and E2 levels also may be associated with feminization or gynecomastia, if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone (GnRH) stimulation test remains the central part of the workup for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels <10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly, in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallman's syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high.

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<tr>
<td>Stage IV</td>
<td>15.1 years</td>
<td>10-46 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-60 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females</td>
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<td>16-77 pg/mL</td>
</tr>
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<td>Stage V</td>
<td>14.5 years</td>
<td>17-200 pg/mL</td>
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# Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-60 pg/mL Females Premenopausal: 17-200 pg/mL Postmenopausal: 7-40 pg/mL Conversion factor E1: pg/mL x 3.704=pmol/L (molecular weight=270) ESTRADIOL (E2) CHILDREN* 1-14 days: Estradiol levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males

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# Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-20 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>Undetectable-24 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>11.6 years</td>
<td>Undetectable-60 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>12.3 years</td>
<td>15-85 pg/mL</td>
</tr>
</tbody>
</table>
Stage V 14.5 years 15-350 pg/mL** #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-40 pg/mL Females Premenopausal: 15-350 pg/mL** Postmenopausal: **E2 levels vary widely through the menstrual cycle. Conversion factor E2: pg/mL x 3.676=pmol/L (molecular weight=272)


E1 81418

Estrone, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25-5 times the biological potency of E1. E2 circulates at 1.5-4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive
assays suffice. However, extra sensitive E2 assays or simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. See Steroid Pathways in Special Instructions.

**Useful For:** As part of the diagnosis and work-up of precocious and delayed puberty in females, and, to a lesser degree, males. As part of the diagnosis and work-up of suspected disorders of sex steroid metabolism, eg, aromatase deficiency and 17 alpha-hydroxylase deficiency. As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men. Monitoring low-dose female hormone replacement therapy in post-menopausal women. Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy).

**Interpretation:** Irregular or absent menstrual periods with normal or high E2 levels (and often high E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women; luteinizing hormone/follicle-stimulating hormone (LH/FSH) should be within the normal range, and E2 levels should ideally be higher than E1 levels. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically <5 pg/mL in these patients. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal male E1 and E2 levels also may be associated with feminization or gynecomastia if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the work-up for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels <10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotropic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1
levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. See Steroid Pathways in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Tanner Stages#</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-16 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>11.5 years</td>
<td>Undetectable-22 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>10-25 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1 years</td>
<td>10-46 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-60 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.</td>
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**Females**

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</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-29 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>10-33 pg/mL</td>
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<tr>
<td>Stage III</td>
<td>11.6 years</td>
<td>15-43 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>12.3 years</td>
<td>16-77 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>14.5 years</td>
<td>17-200 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-60 pg/mL Females Premenopausal: 17-200 pg/mL Postmenopausal: 7-40 pg/mL Conversion factor E1: pg/mL x 3.704=pmol/L (molecular weight=270)</td>
</tr>
</tbody>
</table>

Ethanol, Blood

Clinical Information: Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL.

Useful For: Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol. Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication.

Interpretation: The presence of ethanol in blood at concentrations >30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels >50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level >80 mg/dL (>0.08%) exceeds Minnesota’s legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level > or =400 mg/dL (> or =0.4%) may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug, and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level >150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

Reference Values:
Not detected (Positive results are quantified.)
  Limit of detection: 10 mg/dL (0.01 g/dL)
  Legal limit of intoxication is 80 mg/dL (0.08 g/dL).
  Toxic concentration is dependent upon individual usage history.
  Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)


Ethanol, Chain of Custody, Blood

Clinical Information: Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL. Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol. Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication. Chain-of-custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of ethanol in blood at concentrations >30 mg/dL (>0.03% or g/dL) is...
generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels >50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level >80 mg/dL (>0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level > or =400 mg/dL (> or =0.4%) may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug, and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level >150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

Reference Values:
Not detected (Positive results are quantified.)
Limit of detection: 10 mg/dL (0.01 g/dL)
Legal limit of intoxication: 80 mg/dL (0.08 g/dL).
Toxic concentration is dependent upon individual usage history.
Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)


Ethanol, Serum

Clinical Information: Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is a blood ethanol concentration 80 mg/dL (0.08 g/dL; 0.08%; 800 mcg/dL). In the context of medical/clinical assessment, serum is submitted for analysis. On average, the serum or serum concentration of the alcohols is 1.2-fold higher than blood. The serum would contain approximately 0.10 g/dL of ethanol in a blood specimen that contains 0.08 g/dL ethanol.

Useful For: Detection of ethanol (ethyl alcohol) in serum to document prior consumption or administration of ethanol. Quantification of the concentration of ethanol in serum correlates with degree of intoxication.

Interpretation: The presence of ethanol in blood at concentrations >30 mg/dL (>0.03% or 0.03 g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels >50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol levels > or =80 mg/dL (> or =0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level > or =400 mg/dL (>0.4%) may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level >150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

Reference Values:
<10 mg/dL
Legal limit of intoxication: > or =80 mg/dL
Critical value: > or =400 mg/dL

**ETHSX** 37041

**Ethosuximide, Serum**

**Clinical Information:** Ethosuximide (Zarontin) is used in the treatment of absence (petit mal) seizures, although valproic acid and methsuximide are used more frequently for this condition. Ethosuximide is completely absorbed from the gastrointestinal tract, reaching a peak plasma concentration in 1 to 7 hours. Approximately 10% to 20% of the drug is excreted unchanged in the urine; the remainder is metabolized by hepatic microsomal enzymes. The volume of distribution of ethosuximide is 0.7 L/kg, and its half-life is 40 to 50 hours. Little ethosuximide circulating in the blood is bound to protein. Ethosuximide produces a barbiturate-like toxicity, characterized by central nervous system and respiratory depression, nausea, and vomiting when the blood level is >150 mcg/mL.

**Useful For:** Monitoring therapy Determining compliance Assessing toxicity

**Interpretation:** Dosage is guided by blood levels; the therapeutic range for ethosuximide is 40 to 100 mcg/mL. Toxic concentration: >150 mcg/mL.

**Reference Values:**
- Therapeutic: 40-100 mcg/mL
- Critical value: >150 mcg/mL

**Clinical References:**

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**ETHO** 80449

**Ethotoin (Peganone)**

**Reference Values:**
- Reference Range: 8.0 - 20.0 ug/mL

Please note: The therapeutic range for ethotoin is not well established.

Many patients respond well to ethotoin concentrations up to 60 ug/mL.

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**ETGX** 63418

**Ethyl Glucuronide Confirmation, Chain of Custody, Urine**

**Clinical Information:** Ethyl glucuronide and ethyl sulfate are minor metabolites of ethanol that are detectable in body fluids following alcohol consumption and, less commonly, following extraneous exposure. Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are direct biomarkers or metabolites of ethanol. EtG and EtS can be detected up to 5 days in urine using a cutoff of 500 ng/mL. (1) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Monitoring abstinence in clinical and justice system settings using ethyl blucuronide and ethyl sulfate as direct biomarkers or metabolites of ethanol This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.
Interpretation: High-positive (>1,000 ng/mL) may indicate heavy drinking the same day or within the past 1 to 2 days, or light drinking the same day. Any concentration, up to 1,000 ng/mL, may indicate previous heavy drinking in the past 1 to 3 days, recent light drinking (<1 day), or recent intense extraneous exposure (<1 day).(2)

Reference Values:
Negative

Cutoff concentrations:
Ethyl Glucuronide: 500 ng/mL


Ethyl Glucuronide Confirmation, Urine

Clinical Information: Ethyl glucuronide and ethyl sulfate are minor metabolites of ethanol which are detectable in body fluids following alcohol consumption and less commonly following extraneous exposure.

Useful For: Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are direct biomarkers or metabolites of ethanol. EtG and EtS can be detected up to 5 days in urine using a cutoff of 500 ng/mL.(1) These biomarkers are often used in monitoring abstinence in clinical and justice system settings.

Interpretation: High positive (>1,000 ng/mL) may indicate: heavy drinking the same day or within the past 1 to 2 days, or light drinking the same day. Any concentration up to 1,000 ng/mL may indicate: previous heavy drinking in the past 1 to 3 days, recent light drinking (<1 day), or recent intense extraneous exposure (<1 day).(2)

Reference Values:
Negative


Ethyl Glucuronide Screen with Reflex, Urine

Clinical Information: This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody’s ability to cross-react with different drugs in the class being screened for. Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days.

Useful For: Screening for drug abuse involving alcohol

Interpretation: This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry; LC-MS/MS) must be used to obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological and psychological effects.

Reference Values:
**Clinical References:**

**Ethyl Glucuronide Screen, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened for. Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days.

**Useful For:** Screening for drug abuse involving alcohol

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological and psychological effects.

**Reference Values:**
Negative
Screening cutoff concentration:
Ethyl Glucuronide: 500 ng/mL

**Clinical References:**

**Ethylene Glycol, Serum**

**Clinical Information:** Ethylene glycol, present in antifreeze products, may be ingested accidentally or for the purpose of inebriation or suicide. Ethylene glycol itself is relatively nontoxic, and its initial central nervous system (CNS) effects resemble those of ethanol. However, metabolism of ethylene glycol
by alcohol dehydrogenase results in the formation of a number of acid metabolites, including oxalic acid and glycolic acid. These acid metabolites are responsible for much of the toxicity of ethylene glycol. Three stages of ethylene glycol overdose occur. Within the first few hours after ingestion, there is transient excitation followed by CNS depression. After a delay of 4 to 12 hours, severe metabolic acidosis develops from accumulation of acid metabolites. Finally, delayed renal insufficiency follows deposition of oxalate in renal tubules. Ethylene glycol toxicity is treated with 4-methylpyrazole (4-MP; fomepizole) or ethanol to saturate the enzyme alcohol dehydrogenase and prevent conversion of ethylene glycol to its toxic metabolites.

**Useful For:** Confirming and monitoring ethylene glycol toxicity

**Interpretation:** Toxic concentrations are \( > \text{ or } = \text{20 mg/dL} \)

**Reference Values:**
Toxic concentration: \( > \text{ or } = \text{20 mg/dL} \)

**Clinical References:**

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**Ethylene Oxide, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**EUCL 82758**

**Eucalyptus, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td></td>
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<td>1</td>
<td>0.35-0.69</td>
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<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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**FECLT 57810**

**Euglobulin Clot Lysis Time**

Current as of July 8, 2016 11:28 am CDT  
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  
Page 761
**Euroglyphus maynei, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**EVEROL**

**Clinical Information:** Everolimus is an immunosuppressive agent derived from sirolimus (rapamycin). Both drugs function via inhibition of mTOR signaling, and share similar pharmacokinetic and toxicity profiles. Everolimus has a shorter half-life than sirolimus, which allows for more rapid achievement of steady-state pharmacokinetics. Everolimus is extensively metabolized, primarily by CYP3A4, thus its use with inducers or inhibitors of that enzyme may require dose adjustment. The most common adverse effects include hyperlipidemia, thrombocytopenia, and nephrotoxicity. Everolimus is useful as adjuvant therapy in renal cell carcinoma and other cancers. It recently gained FDA approval for prophylaxis of graft rejection in solid organ transplant, an application which has been accepted for years in Europe. The utility of therapeutic drug monitoring has not been established for everolimus as an oncology chemotherapy agent; however, measuring blood drug concentrations is common practice for its use in transplant. Therapeutic targets vary depending on the transplant site and institution protocol. Guidelines for heart and kidney transplants suggest that trough (immediately prior to the next scheduled dose) blood concentrations between 3 and 8 ng/mL provide optimal outcomes.

**Useful For:** Management of everolimus immunosuppression in solid organ transplant

**Interpretation:** Therapeutic targets vary by transplant site and institution protocol. Heart and kidney transplant guidelines suggest a therapeutic range of 3 to 8 ng/mL. Measurement of drug concentrations in oncology chemotherapy is less common, thus no therapeutic range is established for this application.

**Reference Values:**
Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.


Ewing Sarcoma (EWS), 22q12 (EWSR1) Rearrangement, FISH, Tissue

Clinical Information: Ewing sarcoma (EWS)/primitive neuroectodermal tumors (PNET) are members of the small, round cell group of tumors that are thought to originate in cells of primitive neuroectodermal origin with variable degrees of differentiation. The small, round cell group of tumors also includes rhabdomyosarcomas, desmoplasic small, round cell tumors, and poorly differentiated synovial sarcomas. Although immunohistochemical markers can be helpful in the correct diagnosis of these tumors, recent molecular studies have shown the specificity of molecular markers in differentiating specific subtypes of small, round blue-cell tumors. Accurate diagnosis of each tumor type is important for appropriate clinical management of patients. Ewing tumors are characterized cytogenetically by rearrangements of the EWSR1 gene at 22q12 with FLI1 at 11q24 (t[11;22]) or ERG at 21q22 (t[21;22]) in 85% and 5% to 10% of Ewing tumors, respectively. Less than 1% of cases may have other fusion partners such as ETV1 at 7p22, E1AF at 17q12, or FEV at 2q33. Detection of these transcripts by reverse transcriptase-PCR (RT-PCR) (EWS, Ewing Sarcoma RT-PCR) that allows specific identification of the t(11;22) and the t(21;22), has greatly facilitated the diagnosis of Ewing tumors. However, if the quality of the available RNA is poor, the results are equivocal, or if a rare translocation partner is present, FISH testing has proven to be useful in identifying the 22q12 EWS gene rearrangement in these tumors.

Useful For: Supporting the diagnosis of Ewing sarcoma (EWS)/primitive neuroectodermal tumor (PNET), myxoid chondrosarcoma, desmoplasic small, round cell tumor, clear cell sarcoma, and myxoid liposarcoma when used in conjunction with an anatomic pathology consultation. An aid in the diagnosis of EWS when reverse transcriptase-PCR results are equivocal or do not support the clinical picture

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the EWSR1 FISH probe set. A positive result is consistent with a diagnosis of Ewing sarcoma (EWS)/primitive neuroectodermal tumors (PNET). A negative result suggests that an EWSR1 rearrangement is not present but does not exclude the diagnosis of EWS/PNET.

Reference Values: An interpretive report will be provided.

**Ewing Sarcoma, by Reverse Transcriptase PCR (RT-PCR)**

**Clinical Information:** Ewing sarcoma (ES) and primitive neuroectodermal tumor (PNET), a closely related tumor, are members of the small round-cell tumor group that also includes rhabdomyosarcoma, synovial sarcoma, lymphoma, Wilms tumor, and desmoplastic small round-cell tumor. ES is the second most common malignant tumor of bone in children and young adults. It is an aggressive osteolytic tumor with a high risk of metastasizing. ES can also present as a soft tissue tumor mass. These tumors are usually bland and undifferentiated with relatively low mitotic indexes, which is misleading in light of the rapid growth commonly observed clinically. While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small round-cell tumor group can be very difficult by light microscopic examination alone, especially true when only small-needle biopsy specimens are available for examination. The use of histochemical and immunohistochemical stains (eg, MIC2 [CD99], desmin, myogenin, myoD1, WT1) can assist in establishing the correct diagnosis, but these markers are not entirely specific for ES/PNET. Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas that are useful in the diagnosis of these lesions.(1-4) The balanced t(11;22)(q24;q12) chromosomal translocation produces the EWSR1-FLI1 fusion transcript and is present in 95% of ES and PNET. Because the EWSR1-FLI1 fusion transcript is a common finding in ES/PNET, in soft tissues these 2 lesions are essentially identical. Less common are the t(21;22)(p22;q12) or EWSR1-ERG transcript, present in <5% of ES/PNET tumors, and the t(7;22)(p22;q12) or EWSR1-FEV transcript, present in <1% of these tumors. These fusion transcripts can be detected by reverse-transcriptase PCR (RT-PCR), by FISH, chromogenic in situ hybridization, or by classical cytogenetic analyses. The RT-PCR and FISH procedures are the most sensitive methods to detect these fusion transcripts.(3)

**Useful For:** Supporting a diagnosis of Ewing sarcoma and primitive neuroectodermal tumors

**Interpretation:** A positive EWSR1-FLI1 or EWSR1-ERG result is consistent with a diagnosis of Ewing sarcoma and primitive neuroectodermal tumor (ES/PNET). Sarcomas other than ES/PNET, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of ES/PNET.

**Reference Values:**
An interpretative report will be provided.


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**F-Actin Ab, IgG, S**

**Clinical Information:** Autoimmune hepatitis (AIH) is caused by chronic inflammation within the liver, resulting in damage to the hepatocytes.(1) Initially, patients with AIH may be clinically asymptomatic, usually identified only through an incidental finding of abnormal liver function tests. At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, and/or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies. There are several autoantibodies associated with AIH, although the most common is anti-smooth muscle antibody (anti-SMA). Anti-SMAs are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of anti-SMAs in the
context of AIH has been identified as filamentous-actin (F-actin).(2) Because the clinical symptoms of AIH are nonspecific, being found in a variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published, and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(3) The combination of autoantibody serology, specifically anti-SMAs and anti-F-Actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis.

**Useful For:** Evaluating patients suspected of having autoimmune hepatitis

**Interpretation:** Seropositivity for anti-F-Actin antibodies is consistent with a diagnosis of autoimmune hepatitis (AIH). A negative result for anti-F-Actin antibodies does not exclude a diagnosis of AIH. In a study conducted at Mayo Clinic, the F-Actin ELISA had a clinical sensitivity of 92.9% when using the manufacturerâ€™s recommended cutoff of 20.0 U. In addition, the F-Actin ELISA had a clinical specificity of 76.7% when using the aforementioned cutoffs. See Supportive Data.

**Reference Values:**
- Negative: <20.0 U
- Weak Positive: 20.0-30.0 U
- Positive: >30.0 U

**Clinical References:**

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**F2-Isoprostanes, Urine**

**Clinical Information:** Oxidative stress results from the generation and overaccumulation of reactive oxygen and nitrogen species and has been shown to damage lipoproteins, lipids, DNA, and proteins. Furthermore, oxidative stress may modulate modifications to these lipoproteins and DNA such that endothelial function and inflammatory processes are altered, ultimately resulting in the initiation and progression of atherosclerosis and cardiovascular disease (CVD). Isoprostanes are a series of prostaglandin-like compounds produced via the free-radical catalyzed peroxidation of arachidonic acid, independent of the cyclooxygenase-derived prostaglandins. F2-isoprostanes are considered the "gold standard" test for quantifying lipid peroxidation/oxidative stress in vivo. 15-F2t-isoprostane (15-F2t-IsoP), also referred to as 8-iso-PGF2 alpha or 8-isoprostane F2 alpha, is 1 of the F2-isoprostanes produced in abundance in vivo and has demonstrated potency as a vasoconstrictor within the vasculature of the heart, brain, lung, and kidneys. Generation of 15-F2t-IsoP induces downstream effects including proliferation of vascular smooth muscle cells and release of endothelin. Additional evidence suggests that F2-isoprostanes may increase aspirin resistance to platelet aggregation within platelets and whole blood. F2-isoprostanes are advantageous over other markers of lipid peroxidation due to their in vivo and in vitro stability and are detectable in a variety of human tissues and biological fluids including plasma, urine, lavage fluid, RBCs, and cerebrospinal fluid. Quantitation of F2-isoprostanes in a random urine specimen is considered to be the most accurate and robust measurement of circulating isoprostanes and is a noninvasive method of assessment.

**Useful For:** The assessment of in vivo lipid peroxidation and considered to be an index of systemic oxidative stress over time

**Interpretation:** Elevated urinary F2-isoprostanes reflect widespread oxidative stress and systemic burden of lipid peroxidation end products. Quantitation of F2-isoprostanes in urine is highly dependent upon the methodology utilized; however, mass spectrometry methods (gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry) assays yield superior sensitivity and analytical specificity compared with immunoassays. F2-isoprostanes demonstrate superior clinical sensitivity compared to other oxidative stress biomarkers but lack clinical specificity for any particular disease. Pharmacological treatment with antioxidant supplementation, hypoglycemic agents in diabetes,
smoking cessation, and weight reduction have all been shown to decrease production of F2-isoprostanes.

Reference Values:
> or =18 years: < or =1.0 ng/mg creatinine
<18 years: not established

Clinical References:

FABRZ 35415

Fabry Disease, Full Gene Analysis

Clinical Information: Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced alpha-Gal A activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual alpha-Gal A activity. Males with <1% alpha-Gal A activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiookeratomas, reduced or absent sweating, and corneal opacity. By middle age, most patients develop renal insufficiency leading to end-stage renal disease, as well as cardiac and cerebrovascular disease. Males with >1% alpha-Gal A activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not have other symptoms of classic Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency later in life. The cardiac variant is not associated with renal failure. Female carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severe. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Mutations in the GLA gene result in deficiency of alpha-Gal A. Most of the mutations identified to date are family specific. Full sequencing of the GLA gene identifies over 98% of the sequence variants in the coding region and splice junctions. In addition, our assay detects the intron 4 mutation common in the Taiwanese population.(1) See Fabry Disease: Newborn Screen-Positive Follow-up algorithm and Fabry Disease Testing Algorithm in Special Instructions.

Useful For: Confirmation of a diagnosis of classic or variant Fabry disease in affected males with reduced alpha-Gal A enzyme activity Carrier or diagnostic testing for asymptomatic or symptomatic females, respectively

Interpretation: All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Clinical References:
**Factor IX Inhibitor Evaluation**

**Clinical Information:** Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

**Useful For:** Detection and titering of coagulation inhibitor to the specific factor requested, primarily factor IX in patients with hemophilia B

**Interpretation:** Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR IX ACTIVITY ASSAY**
- Adults: 65-140%
- Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%), which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR IX INHIBITOR SCREEN**
- Negative

**BETHESDA TITER**
- 0 Units

**Clinical References:**

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**Factor IX Known Mutation Sequencing**

**Reference Values:**
- Only orderable as a reflex at order entry for unit code FIXKM / Hemophilia B, Factor IX Gene Known Mutation Screening (Carrier Detection).

**Factor IX Mut Scrn Gene Sequencing**

**Reference Values:**
- Only orderable as a reflex at order entry for test FIXMS / Hemophilia B, Factor IX Gene Mutation Screening.

**Factor V Leiden (R506Q) Mutation, Blood**

**Clinical Information:** Venous thromboembolism includes deep vein thrombosis and its complication, pulmonary embolism. Plasma from 12% to 20% of venous thromboembolism patients is resistant to the anticoagulant effect of activated protein C (APC resistance). Essentially all patients with hereditary APC resistance have a single nucleotide mutation of the coagulation factor V (fV) gene (F5 rs6025), which encodes for an arginine (R) to glutamine (Q) substitution at position 506 of the factor V protein (fV R506Q). The factor V Leiden (R506Q) gene mutation test is a direct mutation analysis of patient blood leukocyte genomic DNA. We recommend the coagulation-based activated protein C (APC)-resistance ratio (mixing with factor V-deficient plasma) as the initial screening assay for APC-resistance. Depending
on the assay system, the APC-resistance ratio may be indeterminate for patients with a lupus anticoagulant or extremely high heparin levels.

**Useful For:** Factor V Leiden mutation testing should be reserved for patients with clinically suspected thrombophilia and: 1) APC-resistance proven or suspected by a low or borderline APC-resistance ratio, or 2) a family history of factor V Leiden.

**Interpretation:** The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (normal, heterozygous fV R506Q, homozygous fV R506Q).

**Reference Values:**

Negative

**Clinical References:**

**Factor VIII Inhibitor Evaluation**

**Clinical Information:** Factor VIII inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Elderly nonhemophilic patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

**Useful For:** Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII

**Interpretation:** Normally, there is no inhibitor, (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR VIII ACTIVITY ASSAY**
- Adults: 55-200%
  - Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR VIII INHIBITOR SCREEN**
- Negative

**BETHESDA TITER**
- 0 Units

**Clinical References:**
**Factor XIII, Qualitative, with Reflex to Factor XIII 1:1 Mix**

**Reference Values:**
- Factor XIII, Qualitative: No Lysis
- Factor XIII, 1:1 Mix: Not Applicable

**False Oat Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**False Ragweed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
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**FDP 35419**

**Familial Dysautonomia, Mutation Analysis, IVS20(+6T->C) and R696P**

**Clinical Information:** Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons. Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal degeneration continues throughout the lifespan. Mutations in the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein gene (IKBKAP) cause the clinical manifestations of familial dysautonomia. The carrier rate in the Ashkenazi Jewish population is 1 in 31. There are 2 common mutations in the Ashkenazi Jewish population: IVS20(+6)T->C and R696P. The carrier detection rate for these 2 mutations is 99%.

**Useful For:** Carrier screening for familial dysautonomia in individuals of Ashkenazi Jewish ancestry

Prenatal diagnosis of familial dysautonomia in at-risk pregnancies Confirmation of a clinical diagnosis of familial dysautonomia in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.
Familial Hypercholesterolemia, LDLR Full Gene Sequencing

**Clinical Information:** Familial hypercholesterolemia (FH) is an autosomal dominant disorder that is characterized by high levels of low-density lipoprotein (LDL) cholesterol and associated with premature cardiovascular disease and myocardial infarction. FH is caused by variants in the LDLR gene, which encodes for the LDL receptor. LDLR variants impair the ability of the LDL receptor to remove LDL cholesterol from plasma via receptor-mediated endocytosis, leading to elevated levels of plasma LDL cholesterol and subsequent deposition in the skin and tendons (xanthomas) and arteries (atheromas). FH can occur in either the heterozygous or homozygous state, with 1 or 2 variant LDLR alleles, respectively. In general, FH heterozygotes have 2-fold elevations in plasma cholesterol and develop coronary atherosclerosis after the age of 30. Homozygous FH individuals have severe hypercholesterolemia (>650 mg/dL) with the presence of cutaneous xanthomas prior to 4 years of age, childhood coronary heart disease, and death from myocardial infarction prior to 20 years of age. Heterozygous FH is prevalent among many different populations, with an approximate average worldwide incidence of 1 in 500 individuals, but as high as 1 in 67 to 1 in 100 individuals in some South African populations and 1 in 270 in the French Canadian population. Homozygous FH occurs at a frequency of approximately 1 in 1,000,000. Treatment is aimed at lowering plasma LDL levels and increasing LDL receptor activity. Identification of LDLR variant(s) in individuals suspected of having FH helps to determine appropriate treatment. FH heterozygotes are often treated with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (ie, statins), either in monotherapy or in combination with other drugs such as nicotinic acid and inhibitors of intestinal cholesterol absorption. Such drugs are generally not effective in FH homozygotes; treatment in these individuals may consist of LDL apheresis, portacaval anastomosis, and liver transplantation. The LDLR gene maps to chromosome 19p13 and consists of 18 exons spanning 45 kb. Hundreds of variants have been identified in the LDLR gene, the majority of them occurring in the ligand binding and epidermal growth factor (EGF) precursor homology regions in the 5' region of the gene (type II and III variants, respectively). The majority of LDLR mutations are missense, small insertion, deletion and other point variants, most of which are detected by full-gene sequencing. Approximately 10% to 15% of LDLR variants are large rearrangements, such as exonic deletions and duplications, which cannot be detected by full-gene sequencing.

**Useful For:** Aiding in the diagnosis of familial hypercholesterolemia (FH) Distinguishing the diagnosis of FH from other causes of hyperlipidemia, such as familial defective apoB-100 and familial combined hyperlipidemia

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
encodes for the LDL receptor. LDLR mutations impair the ability of the LDL receptor to remove LDL cholesterol from plasma via receptor-mediated endocytosis, leading to elevated levels of plasma LDL cholesterol and subsequent deposition in the skin and tendons (xanthomas) and arteries (atheromas). FH can occur in either the heterozygous or homozygous state, with 1 or 2 mutant LDLR alleles, respectively. In general, FH heterozygotes have 2-fold elevations in plasma cholesterol and develop coronary atherosclerosis after the age of 30. Homozygous FH individuals have severe hypercholesterolemia (>650 mg/dL) with the presence of cutaneous xanthomas prior to 4 years of age, childhood coronary heart disease, and death from myocardial infarction prior to 20 years of age. Heterozygous FH is prevalent among many different populations, with an approximate average worldwide incidence of 1 in 500 individuals, but as high as 1 in 67 to 1 in 100 individuals in some South African populations and 1 in 270 in the French Canadian population. Homozygous FH occurs at frequency of approximately 1 in 1,000,000. Treatment is aimed at lowering plasma LDL levels and increasing LDL receptor activity. Identification of LDLR mutation(s) in individuals suspected of having FH helps to determine appropriate treatment. FH heterozygotes are often treated with 3-hyroxy-3-methylglutaryl CoA reductase inhibitors (ie, statins), either in monotherapy or in combination with other drugs such as nicotinic acid and inhibitors of intestinal cholesterol absorption. Such drugs are generally not effective in FH homozygotes; treatment in these individuals may consist of LDL apheresis, portacaval anastomosis, and liver transplantation. The LDLR gene maps to chromosome 19p13 and consists of 18 exons spanning 45 kb. Hundreds of mutations have been identified in the LDLR gene, the majority of them occurring in the ligand binding and epidermal growth factor (EGF) precursor homology regions in the 5' region of the gene (type II and III mutations, respectively). The majority of LDLR mutations are missense, small insertion, deletion, and other point mutations, most of which are detected by full-gene sequencing. Approximately 10% to 15% of LDLR mutations are large rearrangements, such as exonic deletions and duplications, which cannot be detected by full-gene sequencing.

**Useful For:** Genetic testing of individuals at risk for known LDLR familial mutation

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Identification of LDLR variant(s) in individuals suspected of having FH helps to determine appropriate treatment. FH heterozygotes are often treated with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (ie, statins), either in monotherapy or in combination with other drugs such as nicotinic acid and inhibitors of intestinal cholesterol absorption. Such drugs are generally not effective in FH homozygotes, and treatment in this population may consist of LDL apheresis, portacaval anastomosis, and liver transplantation. The LDLR gene maps to chromosome 19p13 and consists of 18 exons spanning 45 kb. Hundreds of variants have been identified in the LDLR gene, the majority of them occurring in the ligand binding and epidermal growth factor (EGF) precursor homology regions in the 5’ region of the gene (type II and III variants, respectively). Although most FH-causing variants are small (eg, point variants), approximately 10% to 15% of variants in the LDLR gene are large rearrangements such as exonic deletions and duplications, which are not amenable to sequencing (eg, LDLRS / Familial Hypercholesterolemia, LDLR Full Gene Sequencing) but can be detected by this MLPA assay.

**Useful For:** Aiding in the diagnosis of familial hypercholesterolemia (FH) in individuals with elevated untreated low-density lipoprotein (LDL) cholesterol Distinguishing the diagnosis of FH from other causes of hyperlipidemia, such as familial defective ApoB-100 and familial combined hyperlipidemia Comprehensive LDL receptor genetic analysis for suspect FH individuals who test negative for an LDLR point variant by sequencing (LDLRS / Familial Hypercholesterolemia, LDLR Full Gene Sequencing)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Familial Hypercholesterolemia/Autosomal Dominant Hypercholesterolemia Genetic Testing Reflex Panel**

**Clinical Information:** Autosomal dominant hypercholesterolemia (ADH) is characterized by high levels of low-density lipoprotein (LDL) cholesterol, and associated with premature cardiovascular disease and myocardial infarction. Approximately 1 in 500 individuals worldwide are affected by ADH. Most ADH is caused by genetic variants leading to decreased intracellular uptake of cholesterol. The majority of these cases have familial hypercholesterolemia (FH), which is due to variants in the LDLR gene, which encodes for the LDL receptor. Approximately 15% of ADH cases have familial defective apolipoprotein B-100 (FDB) due to variants in the LDL receptor-binding domain of the APOB gene, which encodes for apolipoprotein B-100. ADH can occur in either the heterozygous or homozygous state, with 1 or 2 mutant alleles, respectively. In general, FH heterozygotes have 2-fold elevations in plasma cholesterol and develop coronary atherosclerosis after the age of 30. Homozygous FH individuals have severe hypercholesterolemia (generally >650 mg/dL) with the presence of cutaneous xanthomas prior to 4 years of age, childhood coronary heart disease, and death from myocardial infarction prior to 20 years of age. Heterozygous FH is prevalent among many different populations, with an approximate average worldwide incidence of 1 in 500 individuals, but as high as 1 in 67 to 1 in 100 individuals in some South African populations and 1 in 270 in the French Canadian population. Homozygous FH occurs at a frequency of approximately 1 in 1,000,000. Similar to FH, FDB homozygotes express more severe disease, although not nearly as severe as FH homozygotes. Approximately 40% of males and 20% of females with an APOB variant will develop coronary artery disease. In general, when compared to FH, individuals with FDB have less severe hypercholesterolemia, fewer occurrences of tendinous xanthoma, and a lower incidence of coronary artery disease. Plasma LDL cholesterol levels in patients with homozygous FDB
are similar to levels found in patients with heterozygous (rather than homozygous) FH. The LDLR gene maps to chromosome 19p13 and consists of 18 exons spanning 45 kb. Hundreds of variants have been identified in the LDLR gene, the majority of them occurring in the ligand binding and epidermal growth factor (EGF) precursor homology regions in the 5' region of the gene. The majority of variants in the LDLR gene are missense, small insertion or deletion variants, and other point variants, most of which are detected by full gene sequencing. Approximately 10% to 15% of variants in the LDLR gene are large rearrangements, such as large exonic deletions and duplications. The APOB gene maps to chromosome 2p. The vast majority of FDB cases are caused by a single APOB variant at residue 3500, resulting in a glutamine substitution for the arginine residue (R3500Q). This common FDB variant occurs at an estimated frequency of 1 in 500 individuals of European descent. A less frequently occurring variant at that same codon, which results in a tryptophan substitution (R3500W), is more prevalent in individuals of Chinese and Malay descent, and has been identified in the Scottish population as well. The R3500W variant is estimated to occur in approximately 2% of ADH cases. Residue 3500 interacts with other apolipoprotein B-100 residues to induce conformational changes necessary for apolipoprotein B-100 binding to the LDL receptor. Thus, variants at residue 3500 lead to a reduced binding affinity of LDL for its receptor. Identification of 1 or more variants in individuals suspected of having ADH helps to determine appropriate treatment of this disease. Treatment is aimed at lowering plasma LDL levels and increasing LDL receptor activity. FH heterozygotes and FDB homozygotes and heterozygotes are often treated with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (ie, statins), either in monotherapy or in combination with other drugs such as nicotinic acid and inhibitors of intestinal cholesterol absorption. Such drugs are generally not effective in FH homozygotes, and treatment in these individuals may consist of LDL apheresis, portacaval anastomosis, and liver transplantation. Screening of at-risk family members allows for effective primary prevention by instituting statin therapy and dietary modifications at an early stage. This test provides a reflex approach to diagnosing the above disorders. The tests can also be separately ordered: -LDLRS / Familial Hypercholesterolemia, LDLR Full Gene Sequencing -LDLM / Familial Hypercholesterolemia, LDLR Large Deletion/Duplication, Molecular Analysis -APOB / Apolipoprotein B-100 Molecular Analysis, R3500Q and R3500W See Familial/Autosomal Dominant Hypercholesterolemia Diagnostic Algorithm in Special Instructions.

**Useful For:** Aiding in the diagnosis of familial hypercholesterolemia defective apoB-100 in individuals with elevated, untreated low-density lipoprotein cholesterol concentrations Distinguishing the diagnosis of autosomal dominant hypercholesterolemia from other causes of hyperlipidemia, such as familial combined hyperlipidemia Genetic evaluation of hypercholesterolemia utilizing a cost-effective, reflex-testing approach

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

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**FMTT 63032**

**Familial Mutation, Targeted Testing**

**Clinical Information:** This test is available to test for the presence of 1 or more mutations previously identified in a family member. Targeted testing is used for diagnostic or predictive testing in cases in which mutations have been previously identified in an affected family member. Targeted testing is available for a specific subset of genes only. Genes Available for Testing ABCD1 ACADM ACADS ACADVL AGXT APC APOA1 APOA2 ARSA ARSB ATP7B AXIN2 BMP1A BTD CASR CDH1 CDKN1C CFTR CHEK2 CPOX CPT2 CTRC FECH FGA FLCN FTCD GAA GALC GALT GBA GLA GNPTAB GNS GRHR PRN GSN HEXA HGSNAT HMBS IDS IDUA LYZ MAPT MECP2 MEFV
MLH1 MLH3 MLYCD MMACHC MMADHC MSH2 MSH6 MUTYH NAGLU NPC1 NPC2 PKHD1 PMS2 PPOX PRSS1 PSAP PTEN RAI1 RET SCD5 SDHB SDHC SDHD SEPT9 SGSH SLC25A20 SMAD4 SMPD1 SPINK1 STK11 SUMF1 TACSTD1/EPICAM TNFRSF1A TP53 TTR UBE3A VHL

Refer to the following resources for information regarding the listed gene targets. GeneReviews-NCBI Bookshelf, available at URL: http://www.ncbi.nlm.nih.gov/books/NBK1116/ or OMIM, available at URL: http://www.omim.org/. Testing may be delayed if the required documentation is not received (ie, patient information sheet).

**Useful For:** Diagnostic or predictive testing for specific conditions when 1 or more mutations have been identified in a family member Carrier screening for individuals at risk for having a mutation that was previously identified in a family member

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**FANCP**

**Fanconi Anemia C Mutation Analysis, IVS4(+4)A->T and 322delG**

**Clinical Information:** Fanconi anemia is an aplastic anemia that leads to bone marrow failure and myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. The proteins encoded by the genes associated with Fanconi anemia may work together to repair DNA damage. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, IVS4(+4)A->T in the FANCC gene has been shown to be common in the Ashkenazi Jewish population. The carrier rate in the Ashkenazi Jewish population is 1 in 89 and the detection rate for this mutation using this assay is >99%. A second FANCC mutation, 322delG, is overrepresented in patients of Northern European ancestry.

**Useful For:** Carrier screening for Fanconi anemia in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of Fanconi anemia in at-risk pregnancies Confirmation of suspected clinical diagnosis of Fanconi anemia in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


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**FATF**

**Fat, Feces**

**Clinical Information:** Fecal lipids include monoglycerides, diglycerides, triglycerides, phospholipids, glycolipids, soaps, sterols, cholestryel esters, and sphingolipids. Steatorrhea (increased fecal excretion of fat) may reflect a number of pancreatic or intestinal disorders, including chronic pancreatitis with or without stone obstruction, cystic fibrosis, neoplasia, Whipple disease, regional enteritis, tuberculous enteritis, gluten-induced enteropathy (celiac disease), Giardia-associated enteropathy, sprue, or the atrophy of malnutrition.
Useful For: Diagnosing fat malabsorption due to pancreatic or intestinal disorders Monitoring
effectiveness of enzyme supplementation in certain malabsorption disorders

Interpretation: Excretion of >7 grams fat/24 hours, when on a diet of 100 to 150 g of fat, is suggestive
of a malabsorption defect. Abnormal results from a random specimen should be confirmed by submission
of a timed collection. Test values for timed fecal fat collections will be reported in terms of g/24 hours;
the duration of the collection may be 24, 48, 72, or 96 hours. Test values for random fecal fat collections
will be reported in terms of percent fat.

Reference Values:
TIMED COLLECTION
> or =18 years: 2-7 g fat/24 hours
Reference values have not been established for patients who are <18 years of age.

RANDOM COLLECTION
All ages: 0-19% fat

Clinical References: 1. Henderson AR, Rinker AD: Gastric, pancreatic, and intestinal function. In
Edited by ME Shils, M Shike, AC Ross, et al. Baltimore, MD, Lippincott Williams and Wilkins, 2006, pp
1143-1151,1227-1234

Fatty Acid Oxidation Probe Assay, Fibroblast Culture

Clinical Information: Mitochondrial fatty acid beta-oxidation plays an important role in energy
production, particularly in skeletal and heart muscle, and in hepatic ketone body formation. Disorders of
fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy,
skeletal myopathy, and cardiomyopathy. Most FAO disorders have a rather similar presentation and their
biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens such as urine organic
acids, plasma acylcarnitines, and fatty acids are influenced by dietary factors and the clinical status of the
patient. This often leads to incomplete diagnostic information or even false-negative results. Enzyme
assays are limited to 1 enzyme per assay, and molecular assays for common mutations are limited by the
frequent occurrence of compound heterozygous patients with uncommon, private mutations that must be
distinguished from unaffected carriers. Furthermore, neither specific enzyme assays nor molecular genetic
testing is available for all of the known defects. The purpose of the in vitro probe assay is to offer
screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions
using fibroblast cultures.

Useful For: In vitro confirmation of biochemical diagnoses of the following fatty acid oxidation
disorders: -Short-chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium-chain acyl-CoA
dehydrogenase (MCAD) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)
developmental -Trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase (VLCAD)
developmental -Carnitine palmitoyl transferase deficiency type II (CPT-II) -Carnitine-acylcarnitine
translocase (CACT) deficiency In addition, the following organic acid disorders can be confirmed by this
assay: -2-Methylbutyryl-CoA dehydrogenase (SBCAD) deficiency -Isobutyryl-CoA dehydrogenase (IBD)
developmental Work is in progress to evaluate the applicability of this assay to the remaining disorders of
fatty acid transport and mitochondrial oxidation.

Interpretation: Abnormal results will include a description of the abnormal profile, in comparison to
normal and abnormal control controls. In addition, the concentration of those acylcarnitine species that
abnormally accumulated in the cell medium are provided and compared to the continuously updated
reference range based on analysis of normal controls. Interpretations of abnormal acylcarnitine profiles
also include information about the results' significance, a correlation to available clinical information,
possible differential diagnoses, recommendations for additional biochemical testing and confirmatory
studies if indicated, name and phone number of contacts who may provide these studies at the Mayo
Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring
physician has additional questions.
**Fatty Acid Profile, Comprehensive (C8-C26), Plasma**

**Clinical Information:** Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. Fatty Acid Oxidation (FAO) Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies thorough a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with FAO disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Enzyme and molecular confirmatory testing is also available for many of the FAO disorders at Mayo Medical Laboratories. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytic acid, and biosynthesis of plasmalogens and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked.
adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy (XALD / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.

**Useful For:** This plasma test is a comprehensive profile that provides information regarding mitochondrial and peroxisomal fatty acid metabolism, and the patient's nutritional status Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

**Interpretation:** An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of phytanic acid (along with normal pristanic acid concentrations) are seen in the Refsum disease (phytanase deficiency). Phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanoic acid, and pipecolic acid, allows differential diagnosis of peroxisomal disorders.

**Reference Values:**

Octanoic Acid, C8:0  
<1 year: 7-63 nmol/mL  
1-17 years: 9-41 nmol/mL  
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1  
<1 year: 0.8-4.8 nmol/mL  
1-17 years: 1.6-6.6 nmol/mL  
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0  
<1 year: 2-62 nmol/mL  
1-17 years: 3-25 nmol/mL  
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1  
<1 year: 0.6-4.8 nmol/mL  
1-17 years: 1.3-5.8 nmol/mL  
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0  
<1 year: 6-190 nmol/mL  
1-17 years: 5-80 nmol/mL  
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2  
<1 year: 0.3-6.5 nmol/mL  
1-17 years: 0.2-5.8 nmol/mL  
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1  
<1 year: 1-46 nmol/mL  
1-17 years: 1-31 nmol/mL  
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0  
<1 year: 30-320 nmol/mL  
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL
Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
> or =1 year: 7-30 nmol/mL

Homo-Gamma-Linolenic Acid, C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
> or =1 year: 4-13 nmol/mL

Docosanoic Acid, C22:0
0.0-96.3 nmol/mL

Nervonic Acid, C24:1
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Tetracosanoic Acid, C24:0
0.0-91.4 nmol/mL

Hexacosenoic Acid, C26:1
<1 year: 0.2-2.1 nmol/mL
> or =1 year: 0.3-0.7 nmol/mL
Hexacosanoic Acid, C26:0
0.00-1.30 nmol/mL

Pristanic Acid, C15:0(CH3)4
< or =4 months: 0.00-0.60 nmol/mL
5-8 months: 0.00-0.84 nmol/mL
9-12 months: 0.00-0.77 nmol/mL
13-23 months: 0.00-1.47 nmol/mL
> or =2 years: 0.00-2.98 nmol/mL

Phytanic Acid, C16:0(CH3)4
< or =4 months: 0.00-5.28 nmol/mL
5-8 months: 0.00-5.70 nmol/mL
9-12 months: 0.00-4.40 nmol/mL
13-23 months: 0.00-8.62 nmol/mL
> or =2 years: 0.00-9.88 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

FAPCP

Fatty Acid Profile, Comprehensive (C8-C26), Serum

Clinical Information: Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. Fatty Acid Oxidation (FAO) Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body’s supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies through a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with FAO disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the work-up and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing via the FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis are also available for many of the FAO disorders at Mayo Medical Laboratories. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.

Useful For: This serum test is a comprehensive profile that provides information regarding mitochondrial and peroxisomal fatty acid metabolism, and the patient’s nutritional status. Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

Interpretation: An increased triene/tetraene ratio is consistent with essential fatty acid deficiency.
Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of serum very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of serum phytanic acid (along with normal pristanic acid concentrations) are seen in the Refsum disease (phytanase deficiency). Serum phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanoic acid and pipecolic acid allow differential diagnosis of peroxisomal disorders.

Reference Values:
Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
<1 year: 1-46 nmol/mL
1-17 years: 1-31 nmol/mL
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
<table>
<thead>
<tr>
<th></th>
<th>&lt;1 year</th>
<th>1-17 years</th>
<th>&gt; or =18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitoleic Acid, C16:1w7</td>
<td>20-1,020 nmol/mL</td>
<td>100-670 nmol/mL</td>
<td>110-1,130 nmol/mL</td>
</tr>
<tr>
<td>Palmitic Acid, C16:0</td>
<td>720-3,120 nmol/mL</td>
<td>960-3,460 nmol/mL</td>
<td>1,480-3,730 nmol/mL</td>
</tr>
<tr>
<td>Gamma-Linolenic Acid, C18:3w6</td>
<td>6-110 nmol/mL</td>
<td>9-130 nmol/mL</td>
<td>16-150 nmol/mL</td>
</tr>
<tr>
<td>Alpha-Linolenic Acid, C18:3w3</td>
<td>10-190 nmol/mL</td>
<td>20-120 nmol/mL</td>
<td>50-130 nmol/mL</td>
</tr>
<tr>
<td>Linoleic Acid, C18:2w6</td>
<td>350-2,660 nmol/mL</td>
<td>1,600-3,500 nmol/mL</td>
<td>2,270-3,850 nmol/mL</td>
</tr>
<tr>
<td>Oleic Acid, C18:1w9</td>
<td>250-3,500 nmol/mL</td>
<td>350-3,500 nmol/mL</td>
<td>650-3,500 nmol/mL</td>
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<tr>
<td>Vaccenic Acid, C18:1w7</td>
<td>140-720 nmol/mL</td>
<td>320-900 nmol/mL</td>
<td>280-740 nmol/mL</td>
</tr>
<tr>
<td>Stearic Acid, C18:0</td>
<td>270-1,140 nmol/mL</td>
<td>280-1,170 nmol/mL</td>
<td>590-1,170 nmol/mL</td>
</tr>
<tr>
<td>EPA, C20:5w3</td>
<td>2-60 nmol/mL</td>
<td>8-90 nmol/mL</td>
<td>14-100 nmol/mL</td>
</tr>
<tr>
<td>Arachidonic Acid, C20:4w6</td>
<td>110-1,110 nmol/mL</td>
<td>350-1,030 nmol/mL</td>
<td>520-1,490 nmol/mL</td>
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<td>Mead Acid, C20:3w9</td>
<td>8-60 nmol/mL</td>
<td>3-24 nmol/mL</td>
<td>7-30 nmol/mL</td>
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</table>
Homo-Gamma-Linolenic Acid, C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
> or =1 year: 4-13 nmol/mL

Docosanoic Acid, C22:0
0.0-96.3 nmol/mL

Nervonic Acid, C24:1
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Tetracosanoic Acid, C24:0
0.0-91.4 nmol/mL

Hexacosanoic Acid, C26:1
<1 year: 0.2-2.1 nmol/mL
> or =1 year: 0.3-0.7 nmol/mL

Hexacosanoic Acid, C26:0
0.00-1.30 nmol/mL

Pristanic Acid, C15:0(CH3)4
< or =4 months: 0.00-0.60 nmol/mL
5-8 months: 0.00-0.84 nmol/mL
9-12 months: 0.00-0.77 nmol/mL
13-23 months: 0.00-1.47 nmol/mL
Phytic Acid, C16:0(CH3)4
< or =4 months: 0.00-5.28 nmol/mL
5-8 months: 0.00-5.70 nmol/mL
9-12 months: 0.00-4.40 nmol/mL
13-23 months: 0.00-8.62 nmol/mL
> or =2 years: 0.00-9.88 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L


Fatty Acid Profile, Essential, Plasma

Clinical Information: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water retention, and growth retardation.
permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones.

**Useful For:** Evaluating the nutritional intake and intestinal absorption of essential fatty acids
Identifying deficiency of essential and other nutritionally beneficial fatty acids Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)

**Interpretation:** Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency

**Reference Values:**

- **Lauric Acid, C12:0**
  - <1 year: 6-190 nmol/mL
  - 1-17 years: 5-80 nmol/mL
  - > or =18 years: 6-90 nmol/mL

- **Myristic Acid, C14:0**
  - <1 year: 30-320 nmol/mL
  - 1-17 years: 40-290 nmol/mL
  - > or =18 years: 30-450 nmol/mL

- **Hexadecenoic Acid, C16:1w9**
  - <1 year: 21-69 nmol/mL
  - 1-17 years: 24-82 nmol/mL
  - > or =18 years: 25-105 nmol/mL

- **Palmitoleic Acid, C16:1w7**
  - <1 year: 20-1,020 nmol/mL
  - 1-17 years: 100-670 nmol/mL
  - > or =18 years: 110-1,130 nmol/mL

- **Palmitic Acid, C16:0**
  - <1 year: 720-3,120 nmol/mL
  - 1-17 years: 960-3,460 nmol/mL
  - > or =18 years: 1,480-3,730 nmol/mL

- **Gamma-Linolenic Acid, C18:3w6**
  - <1 year: 6-110 nmol/mL
  - 1-17 years: 9-130 nmol/mL
  - > or =18 years: 16-150 nmol/mL

- **Alpha-Linolenic Acid, C18:3w3**
  - <1 year: 10-190 nmol/mL
  - 1-17 years: 20-120 nmol/mL
  - > or =18 years: 50-130 nmol/mL

- **Linoleic Acid, C18:2w6**
  - < or =31 days: 350-2,660 nmol/mL
  - 32 days-11 months: 1,000-3,300 nmol/mL
  - 1-17 years: 1,600-3,500 nmol/mL
  - > or =18 years: 2,270-3,850 nmol/mL

- **Oleic Acid, C18:1w9**
  - <1 year: 250-3,500 nmol/mL
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Vaccenic Acid, C18:1w7
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Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
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DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
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DPA, C22:5w6
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<1 year: 2-20 nmol/mL
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Nervonic Acid, C24:1w9
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> or =18 years: 60-100 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
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Total Saturated Acid
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Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
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Identifying deficiency of essential and other nutritionally beneficial fatty acids
Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)

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</tr>
<tr>
<td>Linoleic Acid, C18:2w6</td>
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<td>1,000-3,300 nmol/mL</td>
<td>1,600-3,500 nmol/mL</td>
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Oleic Acid, C18:1w9  
<1 year: 250-3,500 nmol/mL  
1-17 years: 350-3,500 nmol/mL  
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7  
<1 year: 140-720 nmol/mL  
1-17 years: 320-900 nmol/mL  
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0  
<1 year: 270-1,140 nmol/mL  
1-17 years: 280-1,170 nmol/mL  
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3  
<1 year: 2-60 nmol/mL  
1-17 years: 8-90 nmol/mL  
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<1 year: 110-1,110 nmol/mL  
1-17 years: 350-1,030 nmol/mL  
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9  
< or =31 days: 8-60 nmol/mL  
32 days-11 months: 3-24 nmol/mL  
1-17 years: 7-30 nmol/mL  
> or =18 years: 7-30 nmol/mL

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1-17 years: 60-220 nmol/mL  
> or =18 years: 50-250 nmol/mL

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1-17 years: 30-90 nmol/mL  
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1-17 years: 10-50 nmol/mL  
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DTA, C22:4w6
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1-17 years: 10-40 nmol/mL  
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Docosenoic Acid, C22:1  
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1-17 years: 4-13 nmol/mL  
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9  
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1-17 years: 0.5-4.4 mmol/L  
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid  
<1 year: 1.1-4.9 mmol/L  
1-17 years: 1.7-5.3 mmol/L  
> or =18 years: 3.2-5.8 mmol/L

Total w3  
<1 year: 0.0-0.4 mmol/L  
1-17 years: 0.1-0.5 mmol/L  
> or =18 years: 0.2-0.5 mmol/L

Total w6  
<1 year: 0.9-4.4 mmol/L  
1-17 years: 1.6-4.7 mmol/L  
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids  
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1-17 years: 4.4-14.3 mmol/L  
> or =18 years: 7.3-16.8 mmol/L

from adipose tissue and converted to ketone bodies through a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with fatty acid oxidation (FAO) disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing via FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis are also available for many of the FAO disorders at Mayo Medical Laboratories.

**Useful For:** Biochemical diagnosis of inborn errors of mitochondrial fatty acid oxidation, including deficiencies of medium-chain acyl-Co-A dehydrogenase, long-chain 3-hydroxyacyl-Co-A dehydrogenase, very long-chain acyl-Co-A dehydrogenase, and glutaric acidemia type 2

**Interpretation:** Fatty acid oxidation disorders are recognized on the basis of disease-specific metabolite patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines).

**Reference Values:**

Octanoic Acid, C8:0
- < 1 year: 7-63 nmol/mL
- 1-17 years: 9-41 nmol/mL
- ≥ 18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
- < 1 year: 0.8-4.8 nmol/mL
- 1-17 years: 1.6-6.6 nmol/mL
- ≥ 18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
- < 1 year: 2-62 nmol/mL
- 1-17 years: 3-25 nmol/mL
- ≥ 18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
- < 1 year: 0.6-4.8 nmol/mL
- 1-17 years: 1.3-5.8 nmol/mL
- ≥ 18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
- < 1 year: 6-190 nmol/mL
- 1-17 years: 5-80 nmol/mL
- ≥ 18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
- < 1 year: 0.3-6.5 nmol/mL
- 1-17 years: 0.2-5.8 nmol/mL
- ≥ 18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
- < 1 year: 1-46 nmol/mL
- 1-17 years: 1-31 nmol/mL
<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>&lt;1 year</th>
<th>1-17 years</th>
<th>&gt; or =18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myristic Acid, C14:0</td>
<td>3-320 nmol/mL</td>
<td>40-290 nmol/mL</td>
<td>30-450 nmol/mL</td>
</tr>
<tr>
<td>Hexadecadienoic Acid, C16:2</td>
<td>4-27 nmol/mL</td>
<td>3-29 nmol/mL</td>
<td>10-48 nmol/mL</td>
</tr>
<tr>
<td>Palmitoleic Acid, C16:1w7</td>
<td>20-1,020 nmol/mL</td>
<td>100-670 nmol/mL</td>
<td>110-1,130 nmol/mL</td>
</tr>
<tr>
<td>Palmitic Acid, C16:0</td>
<td>720-3,120 nmol/mL</td>
<td>960-3,460 nmol/mL</td>
<td>1,480-3,730 nmol/mL</td>
</tr>
<tr>
<td>Linoleic Acid, C18:2w6</td>
<td>350-2,660 nmol/mL</td>
<td>1,000-3,300 nmol/mL</td>
<td>2,270-3,850 nmol/mL</td>
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<tr>
<td>Oleic Acid, C18:1w9</td>
<td>250-3,500 nmol/mL</td>
<td>350-3,500 nmol/mL</td>
<td>650-3,500 nmol/mL</td>
</tr>
<tr>
<td>Stearic Acid, C18:0</td>
<td>270-1,140 nmol/mL</td>
<td>280-1,170 nmol/mL</td>
<td>590-1,170 nmol/mL</td>
</tr>
</tbody>
</table>

cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects males; however, some females who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, pipecolic acid (PIPA / Pipecolic Acid, Serum; PIPU / Pipecolic Acid, Urine), phytanic acid and its metabolite pristanic acid. In addition, confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.

**Useful For:** Evaluating patients with possible peroxisomal disorders, including peroxisomal biogenesis disorders, X-linked adrenoleukodystrophy, and Refsum disease An aid in the assessment of peroxisomal function

**Interpretation:** Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0, and phytanic acid:pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, we also include the calculated value of a discriminating function used to more accurately segregate hemizygous individuals from normal controls. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

**Reference Values:**

C22:0  
< or = 96.3 nmol/mL

C24:0  
< or = 91.4 nmol/mL

C26:0  
< or = 1.30 nmol/mL

C24:0/C22:0 RATIO  
< or = 1.39

C26:0/C22:0 RATIO  
< or = 0.023

PRISTANIC ACID  
0-4 months: < or = 0.60 nmol/mL  
5-8 months: < or = 0.84 nmol/mL  
9-12 months: < or = 0.77 nmol/mL  
13-23 months: < or = 1.47 nmol/mL  
> or = 24 months: < or = 2.98 nmol/mL
POX
81369

Fatty Acid Profile, Peroxisomal (C22-C26), Serum

Clinical Information: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogens and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders that are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects males; however, some females who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, pipecolic acid (PIPA), and its metabolite pristanic acid. In addition, confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.
Useful For: Evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy or peroxisomal biogenesis disorders (Zellweger syndrome spectrum) An aid in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0, and phytanic acid:pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, serum phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, we also include the calculated value of a discriminating function used to more accurately segregate hemizygous individuals from normal controls. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

Reference Values:

C22:0  
< or = 96.3 nmol/mL

C24:0  
< or = 91.4 nmol/mL

C26:0  
< or = 1.30 nmol/mL

C24:0/C22:0 RATIO  
< or = 1.39

C26:0/C22:0 RATIO  
< or = 0.023

PRISTANIC ACID  
0-4 months: < or = 0.60 nmol/mL
5-8 months: < or = 0.84 nmol/mL
9-12 months: < or = 0.77 nmol/mL
13-23 months: < or = 1.47 nmol/mL
> or = 24 months: < or = 2.98 nmol/mL

PHYTANIC ACID  
0-4 months: < or = 5.28 nmol/mL
5-8 months: < or = 5.70 nmol/mL
9-12 months: < or = 4.40 nmol/mL
13-23 months: < or = 8.62 nmol/mL
> or = 24 months: < or = 9.88 nmol/mL

PRISTANIC/PHYTANIC ACID RATIO  
0-4 months: < or = 0.35
5-8 months: < or = 0.28
9-12 months: < or = 0.23
13-23 months: < or = 0.24
> or = 24 months: < or = 0.39

**FBN1 Genetic Analysis, Known Mutation**

**Clinical Information:** Fibrillin-1 is a 320-kD cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils that provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the FBN1 gene, which contains 65 exons and is located at chromosome 15q21. FBN1 mutations are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic dilation and aortic aneurysm and dissection, as well as mitral valve and tricuspide valve prolapse. There is significant inter- and intrafamilial variability in phenotype. FBN1 mutations have also been reported in several other rare phenotypes with variable overlap with classic MFS. These conditions include neonatal MFS, autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissection, isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis [premature ossification and closure of sutures of the skull]), and autosomal dominant Weill-Marchesani syndrome (short stature and short fingers, ectopia lentis). Hundreds of mutations have been identified in FBN1, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among FBN1 mutations. Approximately two thirds of FBN1 mutations are missense mutations, with the majority of these being cysteine substitutions. Approximately 25% to 33% of FBN1 mutations are de novo mutations, in which an individual has no family history of disease. FBN1 mutations have been shown to occur across the gene with very few genotype-phenotype correlations, with the exception of the association of neonatal MFS and mutations in exons 24 through 32. Genetic testing for FBN1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of MFS or other FBN1-associated genetic diseases allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Genetic testing of individuals at risk for a known FBN1 mutation

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FBN1, Full Gene Sequence**

**Clinical Information:** Fibrillin-1 is a 320-kD cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils, which provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the FBN1 gene, which contains 65 exons and is located at chromosome 15q21. FBN1 mutations are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular
manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic dilation and aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse. There is significant inter- and intrafamilial variability in MFS phenotype. FBN1 mutations have also been reported in several other rare phenotypes with variable overlap with classic MFS. These conditions include neonatal MFS, autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissection, isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis). Hundreds of mutations have been identified in FBN1, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among FBN1 mutations. Approximately two thirds of FBN1 mutations are missense mutations, with the majority of these being cysteine substitutions. Approximately 25% to 33% of FBN1 mutations are de novo mutations, in which an individual has no family history of disease. FBN1 mutations have been shown to occur across the gene with very few genotype-phenotype correlations, with the exception of the association of neonatal MFS and mutations in exons 24 through 32. Genetic testing for FBN1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of MFS or other FBN1-associated genetic diseases allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Aiding in the diagnosis of FBN1-associated Marfan syndrome, neonatal Marfan syndrome, autosomal dominant ectopia lentis, isolated ascending aortic aneurysm and dissection, isolated skeletal features of Marfan syndrome, MASS phenotype, Shprintzen-Goldberg syndrome, and autosomal dominant Weill-Marchesani syndrome

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**FBNN 89314**

**FBN1, Partial Gene Sequence, Neonatal Marfan Syndrome**

**Clinical Information:** Fibrillin-1 is a 320-kD cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils, which provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the FBN1 gene, which contains 65 exons and is located at chromosome 15q21. FBN1 mutations are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic dilation and aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse. There is significant inter- and intrafamilial variability in phenotype. Neonatal MFS is characterized by a more severe and rapidly progressing phenotype compared with classic MFS. Features can include congenital contractures, dilated cardiomyopathy, congestive heart failure, pulmonary emphysema, and mitral or tricuspid valve regurgitation in the newborn period. The majority of mutations associated with neonatal MFS occur in exons 24 through 32. FBN1 mutations have also been reported in several other rare phenotypes with variable overlap with classic MFS. These conditions include autosomal dominant ectopia...
lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissection, isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis [premature ossification and closure of sutures of the skull]), and autosomal dominant Weill-Marchesani syndrome (short stature and short fingers, ectopia lentis). Hundreds of mutations have been identified in FBN1, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among FBN1 mutations. Approximately two thirds of FBN1 mutations are missense mutations, with the majority of these being cysteine substitutions. Approximately 25% to 33% of FBN1 mutations are de novo mutations, in which an individual has no family history of disease. Genetic testing for FBN1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of neonatal MFS or other FBN1-associated genetic diseases allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Aiding in the diagnosis of neonatal Marfan syndrome

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FETH2 81880**

**Feather Panel # 2**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

FFAPL 57379

Febrile Antibodies Panel

Reference Values:
Rickettsia (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers
Reference Range: Not Detected

Rickettsia (RMSF) Antibodies (IgG, IgM) with Reflex to Titers
Reference Range: Not Detected

Salmonella Antibodies, EIA
Reference Range: Not Detected

Antibodies to Salmonella flagellar (H) and somatic (O) antigens typically peak 3–5 weeks after infection. A positive result in this assay is equivalent to a titer of ≥1:160 by tube agglutination (Widal). Results should not be considered as diagnostic unless confirmed by culture.

Brucella Antibodies (IgG, IgM), EIA with Reflex to Agglutination
Reference Range: <0.80

Interpretive Criteria:
- <0.80 Antibody not detected
- 0.80 ≤< 1.09 Equivocal
- > or = 1.10 Antibody detected

Acute brucellosis is characterized by the appearance of Brucella-specific IgM within the first week of infection, followed by the appearance of Brucella-specific IgG after the second week. Levels of both IgM and IgG decline slowly over several months in conjunction with recovery. Persistence of high IgG levels with declining or absent IgM suggests chronic infection or relapse.

LEU 8046

Fecal Leukocytes

Clinical Information: Leukocytes are not normally seen in stools in the absence of infection or other inflammatory processes. Fecal leukocytosis is a response to infection with microorganisms that invade tissue or produce toxins, which causes tissue damage. Fecal leukocytes are commonly found in patients with shigellosis and salmonellosis (erythrocytes) and sometimes in amebiasis. Mononuclear cells are found in typhoid fever. Ulcerative colitis may also be associated with fecal leukocytosis.

Useful For: Suggesting presence of pathogens such as Salmonella, Shigella, and amebiasis

Interpretation: When fecal leukocytes are found they are reported in a semiquantitative manner: "few" indicates < or = 2/oil immersion microscopic field (OIF); "moderate" indicates 3/OIF to 9/OIF; "many" indicates > or = 10/OIF. The greater the number of leukocytes, the greater the likelihood that an invasive pathogen is present. The finding of many fecal leukocytes is a good indicator of the presence of an
invasive microbiological pathogen such as Salmonella or Shigella. Few or no leukocytes and many erythrocytes suggests amebiasis. Fecal leukocytes are rarely seen in diarrheas caused by other parasites or viruses.

**Reference Values:**
Interpretive report


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FOBT

**60693**

**Fecal Occult Blood, Colorectal Cancer Screen, Qualitative, Immunochemical**

**Clinical Information:** Colorectal cancer (CRC) is 1 of the most commonly diagnosed cancers in the United States (US), and the second leading cause of cancer-related deaths. CRC almost always develops from adenomatous polyps, yet patients remain asymptomatic until the cancer progresses to a fairly advanced stage. Screening for colorectal cancer is strongly advocated for by the US Preventive Services Task Force, the American Cancer Society, the American College of Gastroenterology, and other clinical societies, due to the high incidence of disease and decrease in mortality with medical intervention. Men and women at average risk for colorectal cancer should be screened at regular intervals beginning at age 50, continuing until age 75. Individuals with certain high-risk factors (age, African-American race, inflammatory intestinal disorders, family history of colon cancer, obesity, diabetes, poor diet) may consider earlier screening strategies. Several options are available for CRC screening and includes fecal occult blood testing (FOBT), sigmoidoscopy, and colonoscopy. FOBT historically utilized guaiac-based tests that identify the presence of hemoglobin based on a nonspecific peroxidase reaction. Guaiac-based FOBT is no longer recommended for cancer screening because it does not detect most polyps and cancers. Furthermore, the false-positive rate with guaiac tests is high if patients do not follow the recommended dietary (withholding notably meat, certain vegetables, iron supplements) or pharmaceutical (withholding nonsteroidal anti-inflammatory drugs, vitamin C) restrictions. Finally, multiple stool collections are needed for optimal interpretation of guaiac-based FOBT results. Fecal immunochemical testing (FIT) has evolved as the preferred occult blood test for colorectal cancer screening due to the lack of specificity and sensitivity of guaiac-based methods. FIT specifically detects the presence of human hemoglobin, eliminating the need for dietary and medication restrictions. For colorectal cancer screening only a single collection is required. The specificity of FIT is routinely >95% with reported sensitivities ranging from 40% to 70% based on the patient population. The clinical specificity of FIT is 97% based on internal studies conducted at Mayo. To evaluate occult GI bleeding in patients with anemia or iron deficiency, the HemoQuant test should be used (HQ / HemoQuant, Feces). Neither FIT nor guaiac testing detects upper gastrointestinal (GI) bleeding because globin and heme are degraded during intestinal transit. In contrast, the HemoQuant test detects occult bleeding equally well from all sources within the GI tract. The HemoQuant test utilizes a specific fluorometric method that will detect any hemoglobin or heme-derived porphyrins in the stool, is very sensitive, and provides quantitative results.

**Useful For:** Colorectal cancer screening Screening for gastrointestinal bleeding

**Interpretation:** This is a quantitative assay but results are reported qualitatively as negative or positive for the presence of fecal occult blood; the cutoff for positivity is 100 ng/mL hemoglobin. The following comments will be reported with the qualitative result for patients >17 years: -Positive results; further testing is recommended if clinically indicated. This test has 97% specificity for detection of lower gastrointestinal bleeding in colorectal cancer. -Negative results; this test will not detect upper gastrointestinal bleeding; HQ / HemoQuant, Feces test should be ordered if clinically indicated.

**Reference Values:**
Negative

This test has not been validated in a pediatric population, results should be interpreted in the context of the patient's presentation.

**Clinical References:** 1. Levin B, Lieberman DA, McFarland B, et al: Screening and Surveillance for...

**Felbamate (Felbatol), Serum**

**Clinical Information:** Felbamate is an anticonvulsant drug approved for treatment of partial seizures with or without secondary generalization in persons >14 years of age. It is also approved for Lennox-Gastout syndrome in children >2 years of age. Felbamate is well absorbed (>90%) and is metabolized by the hepatic cytochrome P450 system. Metabolites lack anticonvulsant activity. The elimination half-life of felbamate ranges from 13 to 23 hours. Optimal response to felbamate is seen with serum concentrations between 30 mcg/mL to 60 mcg/mL. Patients who are elderly or have renal dysfunction may require reduced dosing; felbamate should not be given to individuals with hepatic disease. Toxicity can be severe, including life-threatening aplastic anemia or liver failure, but no defined toxic concentration has been established. Coadministration of felbamate increases the concentration of phenytoin and valproic acid, decreases carbamazepine concentration, and increases carbamazepine-10,11-epoxide (its active metabolite). Conversely, coadministration of phenytoin or carbamazepine causes a decrease in felbamate concentration.

**Useful For:** Determining whether a poor therapeutic response is attributable to noncompliance or lack of drug effectiveness Monitoring changes in serum concentrations resulting from interactions with coadministered drugs such as barbiturates and phenytoin

**Interpretation:** Optimal response to felbamate is associated with serum concentrations of 30 mcg/mL to 60 mcg/mL. Toxic serum concentrations for felbamate have not been established.

**Reference Values:**
30.0-60.0 mcg/mL


**Fennel Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Fentanyl and Metabolite, Chain of Custody, Serum

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines,(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids (1); it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.(1,3) Fentanyl is approximately 80% to 85% protein bound.(1) Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The mean elimination half-life is: (1-3) -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys), terminal half-life: 16 hours -Transdermal patch: 17 hours (range 103-22 hours, half-life is influenced by absorption rate) -Transmucosal: - Lozenge: 7 hours - Buccal tablet - 100 mcg to 200 mcg: 3 to 4 hours - 400 mcg to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. In additions to analgesia, alteratons in mood, euphoria, dysphoria, and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Monitoring fentanyl therapy Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the
specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Both fentanyl and norfentanyl are reported. Tolerant individuals may require many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate interpretation of therapeutic drug monitoring (TDMA) results and establishment of a therapeutic window. Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

**Reference Values:**
Not applicable

**Clinical References:**

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**FENR 63061 Fentanyl Screen with Reflex, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened for.

**Useful For:** Screening for drug abuse or use involving fentanyl

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
Negative

Screening cutoff concentration:
- Fentanyl: 2 ng/mL

**Clinical References:**

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**FENS 63060 Fentanyl Screen, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened for.

**Useful For:** Screening for drug abuse or use involving fentanyl

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to
obtain a confirmed analytical result.

Reference Values:
Negative
Screening cutoff concentration:
Fentanyl: 2 ng/mL


Fentanyl with Metabolite Confirmation, Chain of Custody, Urine

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate) -Transmucosal: -Lozenge: 7 hours -Buccal tablet -100 mcg to 200 mcg: 3 to 4 hours -400 mcg to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and confirmation of illicit drug use involving fentanyl Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of fentanyl >0.20 ng/mL or norfentanyl >1.0 ng/mL is a strong indicator that the patient has used fentanyl.

Reference Values:
Negative

Cutoff concentrations:
Immunoassay screen <2 ng/mL
Fentanyl by LC-MS/MS 0.2 ng/mL
Norfentanyl by LC-MS/MS 1.0 ng/mL

Fentanyl with Metabolite Confirmation, Urine

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate) -Transmucosal: - Lozenge: 7 hours - Buccal tablet - 100 to 200 mcg: 3 to 4 hours - 400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

Useful For: Detection and confirmation of illicit drug use involving fentanyl

Interpretation: The presence of fentanyl >0.20 ng/mL or norfentanyl >1.0 ng/mL is a strong indicator that the patient has used fentanyl.

Reference Values:
Negative


Fentanyl, Serum

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound.(1) Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the
observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of
the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The
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half-life: 16 hours -Transdermal patch: 17 hours (range 103-22 hours, half-life is influenced by absorption
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nervous system. In additions to analgesia, alterations in mood, euphoria, dysphoria, and drowsiness
commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other
opioids, fentanyl has become a popular drug of abuse.

Useful For: Monitoring fentanyl therapy

Interpretation: Both fentanyl and norfentanyl are reported. Tolerant individuals may require
many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate
interpretation of therapeutic drug monitoring (TDMA) results and establishment of a therapeutic window.
Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

Reference Values:
Not applicable

Gilman’s The Pharmacological Basis of Therapeutics. Vol 11. Edited by JG LL Hardman, AG Gilman,
187-205 3. Package insert: DURAGESIC (fentanyl transdermal system. Pharmaceutical Products, LP,
Biochemical Publications. 2008 pp 616-619

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82143

Ferret Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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</table>

Ferritin, Serum

Clinical Information: Ferritin is a large spherical protein consisting of 24 noncovalently linked subunits with a molecular weight of approximately 450,000 daltons. The subunits form a shell surrounding a central core containing variable amounts of ferric hydroxyphosphate. One molecule of ferritin is capable of binding between 4,000 and 5,000 atoms of iron, making ferritin the major iron storage protein for the body. Ferritin is found chiefly in the cytoplasm of cells of the reticuloendothelial system and is a constituent of normal human serum. The concentration of ferritin is directly proportional to the total iron stores in the body, resulting in serum ferritin concentrations becoming a common diagnostic tool in the evaluation of iron status. In most normal adults, serum ferritin concentrations vary with age and sex. There is a sharp rise in serum ferritin concentrations in the first month of life, coinciding with the depression of bone marrow erythropoiesis. Within 2 or 3 months, erythropoiesis becomes reactivated and there is a drop in the concentration of serum ferritin. By 6 months, the concentration is reduced to fairly low levels where they remain throughout childhood. There is no sex difference until the onset of puberty, at which time ferritin concentrations rise, particularly in males. There is a significant positive correlation between age and serum ferritin concentrations in females, but not in males. Patients with iron deficiency anemia have serum ferritin concentration approximately one-tenth of normal subjects, while patients with iron overload (hemochromatosis, hemosiderosis) have serum ferritin concentrations much higher than normal. Studies also suggest that serum ferritin provides a sensitive means of detecting iron deficiency at an early stage. Serum ferritin concentrations may serve as a tool to monitor the effects of iron therapy, but results should be interpreted with caution, as these cases may not always reflect the true state of iron stores. Ferritin is a positive acute phase reactant in both adults and children, whereby chronic inflammation results in a disproportionate increase in ferritin in relation to iron reserves. Elevated ferritin is also observed in acute and chronic liver disease, chronic renal failure, and in some types of neoplastic disease. Evaluating body iron stores may include serum iron determination, total iron binding capacity (TIBC), and percent saturation of transferrin, however are subject to diurnal variations and may be less precise. Additionally, they do not discriminate between depleted iron stores (iron deficiency) and conditions associated with defective iron release (eg, anemia of chronic disease).

Useful For: Aiding in the diagnosis of iron deficiency and iron overload conditions Differentiating iron deficiency anemia and anemia of chronic disease

Interpretation: Hypoferritinemia is associated with increased risk for developing iron deficiency where iron deficiency is sufficient to reduce erythropoiesis causing hemoglobin concentrations to fall. Latent iron deficiency occurs when serum ferritin is low without low hemoglobin. Hyperferritinemia is associated with iron overload conditions including hereditary hemochromatosis where concentrations may exceed 1,000 mcg/L. Non-iron overload hyperferritinemia may be caused by common liver disorders, neoplasms, acute or chronic inflammation, and hereditary hyperferritinemia-cataract syndrome. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

Reference Values:
Males: 24-336 mcg/L
Females: 11-307 mcg/L


**FECHZ**

**Ferrochelatase (FECH) Gene, Full Gene Analysis**

**Clinical Information:** Erythropoietic protoporphyria (EPP) is an inherited disorder of porphyrin metabolism whose clinical manifestations include painful photodermatosis without blisters and liver disease. The disorder results from decreased activity of the enzyme ferrochelatase (FECH). FECH is the last of 8 enzymes acting sequentially in the heme biosynthetic pathway and is encoded by the FECH gene located on chromosome 18. The skin symptoms in EPP include immediate painful photosensitivity, usually beginning in early infancy upon sun exposure. Repeated photosensitivity episodes result in skin thickening and areas of hyperkeratosis. This is typically noted on areas where sun exposure is most common, such as the dorsa of the hands and on the face. A small number of patients with EPP develop liver complications. Hepatic disease in EPP may include cholelithiasis and chronic liver disease progressing to rapid acute liver failure. Biochemically, EPP is characterized by elevated protoporphyrin levels in red blood cells, which fluorescence under Wood's light due to the accumulation of free protoporphyrin IX. Protoporphyrin elevations may also be found in plasma and stool, but not in all patients. Urine protoporphyrin levels are usually normal unless there is liver involvement. Studies have also suggested that a reduction in activity of ferrochelatase to <50% of normal levels can induce clinical manifestations. The gold standard test for the diagnosis of EPP is biochemical analysis (PEE / Porphyrins Evaluation, Whole Blood), interpreted in the context of clinical features. In most patients with EPP, a pathogenic FECH mutation that reduces enzyme activity by 50% can be identified on only 1 allele. Clinical expression of EPP typically requires a hypomorphic (low expression) FECH allele (IVS3-48T->C) in trans (on a different chromosome) with the mutation. IVS3-48T->C is a variant of the FECH gene associated with reduced gene expression. This variant is found in approximately 10% of the general Caucasian population. Autosomal recessive inheritance (2 pathogenic mutations in trans) is infrequent, accounting for <4% of EPP cases. In contrast to patients with 1 pathogenic mutation and the low-expression allele, missense mutations are far more common than null mutations. It is uncertain whether protoporphyrin liver failure is more common among individuals with a single null (splicing defect, nonsense, or frameshift) mutation than those with 2 pathogenic mutations as some literature has suggested. In any case, it is certain that all EPP patients should be monitored for hepatic disease and actively manage their photosensitivity.

**Useful For:** Confirmation of a diagnosis of erythropoietic protoporphyria (EPP) following positive biochemical genetic test results obtained through PEE / Porphyrins Evaluation, Whole Blood Carrier testing for individuals with a family history of EPP in the absence of known mutations in the family

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

Fetal Lung Profile, Amniotic Fluid

**Clinical Information:** Respiratory distress syndrome is a common complication of prematurity occurring in infants whose lungs lack the surfactant necessary for healthy lung inflation and air exchange. Surfactant is not produced in sufficient quantity until relatively late in gestation. It is primarily made up of phospholipids such as lecithin and phosphatidylglycerol, which can be detected in amniotic fluid and used as markers for fetal lung maturity. Both the lecithin/sphingomyelin (L/S) ratio and phosphatidylglycerol (PG) concentration increase with gestational age and correlate with lung maturity. Testing both the L/S ratio and the presence or absence of PG provides a better assessment of neonatal risk than the use of either test alone.

**Useful For:** Determining the ability of fetal lungs to produce sufficient quantities of pulmonary surfactant Assessing the risk of developing neonatal respiratory distress in fetuses delivered less than 39 weeks gestational age

**Interpretation:**
- L/S ratio <2.5 and PG absent: immature
- L/S ratio > or =2.5 and PG absent: indeterminate
- L/S ratio <2.5 and PG trace: indeterminate
- L/S ratio > or =2.5 and PG trace: mature
- PG present: mature

**Reference Values:**

<table>
<thead>
<tr>
<th>Lecithin/ Sphingomyelin Ratio</th>
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</thead>
<tbody>
<tr>
<td>Absent</td>
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<tr>
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<td>Indeterminate</td>
</tr>
<tr>
<td>Trace</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>&gt; or =2.5</td>
<td>Trace</td>
</tr>
<tr>
<td>Any ratio</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>Mature</td>
</tr>
</tbody>
</table>

All results will be called back.

**Clinical References:**

Fetomaternal Bleed, Flow Cytometry, Blood

**Clinical Information:** In hemolytic disease of the newborn, fetal red cells become coated with IgG alloantibody of maternal origin, directed against an antigen on the fetal cells that is of paternal origin and absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage (FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen.(1)

1. Rh immune globulin (RhiG, anti-D antibody) is given to Rh-negative mothers who are pregnant with an Rh-positive fetus. Anti-D antibody binds to fetal D-positive red cells, preventing development of the maternal immune response. RhiG can be given either
before or after delivery. The volume of FMH determines the dose of RhIG to be administered.

**Useful For:** Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin

**Interpretation:** Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300 mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBCs. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects. The effectiveness of RhIG decreases beyond 72 hours post exposure but may still be clinically warranted. This assay has been validated out to 5 days post collection.

**Reference Values:**
< or =1.5 mL of fetal RBCs in normal adults

**Clinical References:**
**FGF1F**

**FGFR1 (8p11.2) Amplification, FISH, Tissue**

**Clinical Information:** Fibroblast growth factor receptor 1 (FGFR1) is a receptor tyrosine kinase. FGFR1 overexpression or amplification in squamous cell carcinoma is associated with tumor growth. Studies have shown overexpression or amplification of FGFR1 to be vulnerable to FGFR-tyrosine kinase inhibitors and FGFR1 inhibitors maybe a promising therapeutic option and have shown tumors with FGFR1 amplification may be sensitive to FGFR1 tyrosine kinase inhibitors.

**Useful For:** Providing prognostic information and guiding treatment primarily for patients with squamous cell carcinoma of the lung, breast, esophagus, thymus, and other locations

**Interpretation:** FGFR1 will be clinically interpreted as positive or negative. The FGFR1 locus is reported as amplified when the FGFR1:D8Z2 ratio is >2.0 or an average of 6 or more copies of the FGFR1 locus are observed per tumor nucleus. A tumor with an FGFR1:D8Z2 ratio < or =2.0 and having an average of <6 copies of FGFR1 per tumor nucleus is considered negative for amplification of the FGFR1 locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FGFRF**

**FGFR1 (8p11.2) Rearrangement, FISH**

**Clinical Information:** The gene for fibroblast growth factor receptor 1 (FGFR1) is located at 8p11.2 and rearrangements of FGFR1 are found in stem cell myeloproliferative disorders involving both lymphoid and myeloid lineages. The stem cell myeloproliferative disorders with FGFR1 rearrangements are also called 8p11 (eight p11) myeloproliferative syndromes (EMS) and have variable presentations. EMS often transform rapidly into myelomonocytic leukemia and generally have a poor outcome due to resistance to current chemotherapies, including imatinib myesylate; median survival is about 12 months. All translocations affecting FGFR1 have a similar structure with a 5' gene partner translocating to the 3' FGFR1 at exon 9. The fusion transcripts encode large proteins containing the N-terminus of the translocation partner, and the tyrosine kinase domain of FGFR1 in the C-terminus. Leukemogenesis is caused by inappropriate activation of FGFR1.

**Useful For:** An aid in identifying patients with myeloproliferative syndromes and the t(8;var)(p11.2;var) translocation who therefore are likely resistant to current chemotherapies

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
FGFR2 (10q26.1) Rearrangement, FISH, Tissue

Clinical Information: Cholangiocarcinoma is a malignancy arising from the biliary tract epithelium. These tumors are often clinically advanced at the time of presentation and the prognosis is very poor with a short overall survival. Treatment is generally limited to surgical resection, which is associated with a high degree of morbidity, and palliative chemotherapy regimens. Therefore, additional treatment options are eagerly sought. Rearrangement of the FGFR2 gene region has been identified in a subset of cholangiocarcinomas. These rearrangements result in overexpression of FGFR2, which offers the possibility of using targeted FGFR2-inhibitor therapy for treatment. FGFR2 rearrangement has been identified in a number of other cancers including those of the bladder, thyroid, oral cavity, and brain. In the future, it is likely that the presence of FGFR2 rearrangements will be exploited in the treatment of these cancers as well.

Useful For: Providing prognostic information and guiding treatment for patients with cholangiocarcinomas and other tumor types including bladder, thyroid, oral cavity, and brain

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the FGFR2 locus and a tumor that may be responsive to targeted FGFR2-inhibitor therapy. A negative result suggests no rearrangement of the FGFR2 gene region at 10q26.1.

Reference Values: An interpretive report will be provided.


Fibrinogen Alpha-Chain (FGA) Gene, Full Gene Analysis

Clinical Information: The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, gelsolin, cystatin C, lysozyme, and fibrinogen alpha chain (FGA). Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as nonneuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. FGA-related familial visceral amyloidosis commonly presents with renal failure, which can often be fulminant, and is characterized by hypertension, proteinuria, and azotemia. Liver and spleen involvement may be seen in advanced cases. Neuropathy is not a feature of FGA-related familial visceral amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser-capture tandem mass spectrometry might serve as a useful test preceding gene
sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clinically clear. It is important to note that there are rare disorders of hemostasis that are also associated with mutations in the FGA gene. Patients with afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia have all been reported to have mutations in FGA. Most dysfibrinogenemias are autosomal dominant disorders; afibrinogenemia and hypofibrinogenemia are more often autosomal recessive disorders. In general, truncating mutations in FGA result in afibrinogenemia and missense mutations are a common cause of dysfibrinogenemia.

**Useful For:** Confirming a diagnosis of fibrinogen alpha-chain (FGA) gene-related familial visceral amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

---

**FIBAG**

**Fibrinogen Antigen, Plasma**

**Clinical Information:** Fibrinogen (clotting factor I) is an essential protein responsible for blood clot formation. In the final step of the coagulation cascade, thrombin converts soluble fibrinogen into insoluble fibrin strands that crosslink and form a clot. Fibrinogen is synthesized in the liver and has a biological half-life of 3 to 5 days in the circulating plasma. Fibrinogen deficiencies can be congenital or acquired and lead to prolonged coagulation times. Isolated fibrinogen deficiency is an extremely rare inherited coagulation disorder. Acquired fibrinogen deficiency is most commonly caused by, acute or decompensated intravascular coagulation and fibrinolysis (DIC). Other causes of fibrinogen deficiency include advanced liver disease, L-asparaginase therapy, or fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator).

**Useful For:** Evaluation of fibrinogen deficiency Measuring fibrinogen in patients with elevated plasma levels of fibrin degradation products, patients receiving heparin, and in patients with antibodies to thrombin (following surgical use of topical bovine thrombin) Identifying afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia when ordered in combination with fibrinogen activity (FIB / Fibrinogen,Plasma)

**Interpretation:** This method measures the total amount of fibrinogen protein (ie, fibrinogen antigen) present in the plasma. Adequate fibrinogen antigen levels in a context of low fibrinogen activity suggests a dysfibrinogenemia. Fibrinogen antigen levels <100 mg/dL are associated with an increased risk of bleeding.

**Reference Values:**
196-441 mg/dL


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**FIB**

**Fibrinogen, Plasma**

Current as of July 8, 2016 11:28 am CDT

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: Fibrinogen, also known as factor I, is a plasma protein that can be transformed by thrombin into a fibrin gel (“the clot”). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is 1 of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include: acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation [DIC]), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely than the acquired to be associated with bleeding or thrombotic disorders. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Congenital dysfibrinogenemias usually are inherited as autosomal codominant traits. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or renal diseases (eg, chronic glomerulonephritis, hypernephroma) and usually are associated with elevated fibrinogen levels. Fibrinogen is an acute phase reactant, so a number of acquired conditions can result in an increase in its plasma level: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial thromboembolism.

Useful For: Detecting increased or decreased fibrinogen (factor I) concentration of acquired or congenital origin Monitoring severity and treatment of disseminated intravascular coagulation and fibrinolysis

Interpretation: This kinetic assay assesses levels of functional (clottable) fibrinogen (see Cautions).

Reference Values:
Males: 200-375 mg/dL
Females: 200-430 mg/dL
In normal, full-term newborns and in healthy, premature infants (30-36 week gestation), fibrinogen is near adult levels and reaches adult levels by ≤ or ≥21 days postnatal.


Fibrinogen (FIBR), 8482

Clinical Information: Cultures of skin fibroblasts are useful for specialized testing, which requires skin cells. These cells can be cultured and tested at Mayo Clinic or sent to external laboratories performing these specialized tests. In addition, cells are frozen for at least 3 years for potential future studies on cultured cells or for molecular genetic testing.

Useful For: A preliminary step in obtaining cultured cells for genetic testing

Reference Values: Not applicable

Clinical References:
**Fibroblast Culture for Genetic Testing**

**Clinical Information:** Fibroblast cells may be used to perform a wide range of laboratory tests. Prior to testing, the tissue may need to be cultured to obtain adequate numbers of cells.

**Useful For:** Producing fibroblast cultures that can be used for genetic analysis Once confluent flasks are established, the fibroblast cultures are sent to other laboratories, either within Mayo Clinic or to external sites, based on the specific testing requested.

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**Fibroblast Growth Factor 23 (FGF23), Plasma**

**Clinical Information:** Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate homeostasis. It may act in concert with several other less well-characterized phosphate regulators. FGF23 is secreted primarily by bone, followed by thymus, heart, brain and, in low levels, by several other tissues. It is coexpressed with the X-linked phosphate-regulating endopeptidase (PHEX). High serum phosphate levels stimulate FGF23 expression and secretion through as yet poorly understood mechanisms. PHEX appears to modulate this process, possibly in part through cleavage of FGF23. Only intact FGF23 is considered bioactive. It interacts with a specific receptor on renal tubular cells, decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased phosphate reabsorption. In addition, gene transcription of 1-a-hydroxylase is downregulated, reducing bioactive 1,25-dihydroxy vitamin D (1,25-2OH-VitD), thereby further decreasing phosphate reabsorption. Eventually, falling serum phosphate levels lead to diminished FGF23 secretion, closing the feedback loop. Measurement of FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism in patients with either normal or impaired renal function. When FGF23 levels are pathologically elevated in individuals with normal renal function, hypophosphatemia, with or without osteomalacia, ensues. This can occur with rare, usually benign, mixed connective tissue tumors that contain characteristic complex vascular structures, osteoclast-like giant cells, cartilaginous elements, and dystrophic calcifications. These neoplasms secrete FGF23 ectopically and autonomously (oncogenic osteomalacia). In less than one-fourth of cases a different benign or malignant, soft tissue tumor type, or, extremely rarely, a carcinoma, may be the cause of paraneoplastic FGF23 secretion. In either scenario, complete removal of the tumor cures the oncogenic osteomalacia. Hypophosphatemia and skeletal abnormalities are also observed in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR). In XLH, mutations of PHEX reduce its negative modulatory effect on bioactive FGF23 secretion. In ADHR, FGF23 mutations render it resistant to proteolytic cleavage, thereby increasing FGF23 levels. However, not all FGF23 mutations increase renal phosphate secretions. Mutations that impair FGF23 signaling, rather than increase its protease resistance, are associated with the syndrome of familial tumoral calcinosis (ectopic calcifications) with hyperparathyreomia. In patients with renal failure, FGF23 contributes to renal osteodystrophy. The patient's kidneys can no longer excrete sufficient amounts of phosphate. This leads to marked increases in FGF23 secretions in a futile compensatory response, aggravating the 1,25-2OH-VitD deficiency of renal failure and the consequent secondary hyperparathyroaidism.

**Useful For:** Diagnosing and monitoring oncogenic osteomalacia Possible localization of occult neoplasms causing oncogenic osteomalacia Diagnosing X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets Diagnosing familial tumoral calcinosis with hyperparathyreomia Predicting treatment response to calcitriol or vitamin D analogs in patients with renal failure

**Interpretation:** The majority of patients with oncogenic osteomalacia have fibroblast growth factor 23 (FGF23) levels >2 times the upper limit of the reference interval. However, since the condition is a rare cause of osteomalacia, a full baseline biochemical osteomalacia workup should precede FGF23 testing. This should include measurements of the serum concentrations of calcium, magnesium, phosphate, alkaline phosphate, creatinine, parathyroid hormone (PTH), 25-hydroxy vitamin D (25-OH-VitD), 1,25-2OH-VitD, and 24-hour urine excretion of calcium and phosphate. Findings suggestive of oncogenic osteomalacia, which should trigger serum FGF23 measurements, are a combination of normal serum calcium, magnesium, and PTH; normal or near normal serum 25-OH-VitD; low or low-normal serum 1,25-2OH-VitD; low-to-profoundly low serum phosphate; and high urinary phosphate excretion. Once oncogenic osteomalacia has been diagnosed, the causative tumor should be sought and removed. Complete removal can be documented by normalization of serum FGF23 levels. Depending on the
magnitude of the initial elevation, this should occur within a few hours to a few days (half-life of FGF23 is approximately 20 to 40 minutes). Persistent elevations indicate incomplete removal of tumor. Serial FGF23 measurements during follow-up may be useful for early detection of tumor recurrence, or in partially cured patients, as an indicator of disease progression. Because FGF23 has a short half-life, selective venous sampling with FGF23 measurements may be helpful in localizing occult tumors in patients with oncogenic osteomalacia. However, the most useful diagnostic cutoff for gradients between systemic and local levels has yet to be established. X-linked hypophosphatemia (XLH) and most cases of autosomal dominant hypophosphatemic rickets (ADHR) present before the age of 5 as vitamin D-resistant rickets. FGF23 is significantly elevated in the majority of cases. Genetic testing provides the exact diagnosis. A minority of patients with ADHR may present later, as older children, teenagers, or young adults. These patients may have clinical features and biochemical findings, including FGF23 elevations, indistinguishable from oncogenic osteomalacia patients. Genetic testing may be necessary to establish a definitive diagnosis. Patients with familial tumoral calcinosis and hyperphosphatemia have loss-of-function FGF23 mutations. The majority of these FGF23 mutant proteins are detected by FGF23 assays. The detected circulating levels are very high, in a futile compensatory response to the hyperphosphatemia. Almost all patients with renal failure have elevated FGF23 levels, and FGF23 levels are inversely related to the likelihood of successful therapy with calcitriol or active vitamin D analogs. Definitive cutoffs remain to be established, but it appears that renal failure patients with FGF23 levels of >50 times the upper limit of the reference range have a low chance of a successful response to vitamin D analogues (<5% response rate).

Reference Values:
Results may be significantly elevated (ie, >900 RU/mL) in normal infants <3 months of age.
3 months-17 years: ≤230 RU/mL
> or =18 years: ≤180 RU/mL

Clinical References:

**FIGE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**FFAG4**

**Interpretive Criteria:**

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<thead>
<tr>
<th>Range</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1:50</td>
<td>Negative</td>
</tr>
<tr>
<td>1.50-3.00</td>
<td>Equivocal</td>
</tr>
<tr>
<td>&gt;3.00</td>
<td>Positive</td>
</tr>
</tbody>
</table>

This assay detects Filaria IgG4 associated with infections caused by the major filarial parasites,
including Dirofilaria immitis, Wuchereria bancrofti, Brugia malayi, and Onchocerca volvulus. Detection of IgG4 subclass antibody offers enhanced specificity without sacrifice of sensitivity. Chronic filarial infections manifesting as elephantiasis may not show a significant IgG4 response, and cannot be ruled out by this assay. Equivocal results may represent cross-reactive antibodies induced by infection with other nematodes.

Filaria, Blood

Clinical Information: Filaria are nematodes (roundworms) which are widespread in nature, especially in tropical areas. The adults produce microscopic microfilariae which can be transmitted to humans by biting insects (mosquitos or blackflies). In the lymphatic filariases, the microfilariae migrate to the lymphatics where they mature to adults and cause obstruction (elephantiasis). Lymphatic filariases caused by Wuchereria bancroftii occurs primarily in Africa and that caused by Brugia malayi occurs in South and East Asia. Treatment with diethylcarbamazine or ivermectin is effective in all but the most advanced stages. In onchocerciasis, adults mature in subcutaneous nodules and release new microfilariae which may migrate to the eye and cause blindness (African River Blindness). Ivermectin use has dramatically improved the outlook for control and treatment of onchocerciasis in Africa.

Useful For: Detection of the microfilariae of the lymphatic filariases (not onchocerciasis) in the peripheral blood by stained smears and/or a concentration technique

Interpretation: Positive results are provided with the genus and species of the microfilariae, if identifiable.

Reference Values:
Negative
If positive, organism is identified.


Finch Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

**Fire Ant, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

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**FBSH**

82735

**Firebush (Kochia), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3.50-17.4</td>
<td>Positive</td>
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<td>17.5-49.9</td>
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<td>Strongly positive</td>
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</tr>
</tbody>
</table>

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**1STT**

87857

**First Trimester Maternal Screen**

**Clinical Information:** Multiple marker serum screening has become a standard tool used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects such as Down syndrome and trisomy 18. Second-trimester multiple marker screening has been well established for over a decade. During 2002 through 2006, first-trimester screening has been established as an alternative
option of equal or better performance compared with the best second-trimester screening programs. The first-trimester screen is performed by measuring analytes in maternal serum that are produced by the fetus and the placenta. Additionally, the nuchal translucency (NT) measurement is a sonographic marker shown to be effective in screening fetuses for Down syndrome. A mathematical model is used to calculate a risk estimate by combining the analyte values, NT measurement, and maternal demographic information. The laboratory establishes a specific cutoff for each condition, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered. Serum Analytes Human chorionic gonadotropin (total beta-hCG): hCG is a glycoprotein consisting of alpha and beta subunits. hCG is synthesized by placental cells starting very early in pregnancy and serves to maintain the corpus luteum and, hence, progesterone production during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with an increased risk for Down syndrome. Pregnancy-associated plasma protein A (PAPP-A): PAPP-A is a 187 kDa protein comprised of 4 subunits: 2 PAPP-A subunits and 2 pro-major basic protein (proMBP) subunits. PAPP-A is a metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4), dramatically reducing IGFBP-4 affinity for IGF1 and IGF2, thereby regulating the availability of these growth factors at the tissue level. PAPP-A is highly expressed in first-trimester trophoblasts, participating in regulation of fetal growth. Levels in maternal serum increase throughout pregnancy. Low PAPP-A levels before the 14th week of gestation are associated with an increased risk for Down syndrome and trisomy 18. Nuchal translucency (NT): The NT measurement, an ultrasound marker, is obtained by measuring the fluid-filled space within the nuchal region (back of the neck) of the fetus. While fetal NT measurements obtained by ultrasonography increase in normal pregnancies with advancing gestational age, Down syndrome fetuses have larger NT measurements than gestational age-matched normal fetuses. Increased fetal NT measurements can therefore serve as an indicator of an increased risk for Down syndrome.

**Useful For:** Prenatal screening for Down syndrome (nuchal translucency, pregnancy-associated plasma protein A, human chorionic gonadotropin) and trisomy 18 (nuchal translucency, pregnancy-associated plasma protein A, human chorionic gonadotropin)

**Interpretation:** Screen-Negative: A screen-negative result indicates that the calculated screen risk is below the established cutoff of 1/230 for Down syndrome and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 18 or Down syndrome. Screen-negative results typically do not warrant further evaluation. Screen-Positive: When a Down syndrome risk cutoff of 1/230 is used for follow-up, the combination of maternal age, pregnancy-associated plasma protein A, human chorionic gonadotropin, and nuchal translucency has an overall detection rate of approximately 85% with a false-positive rate of 5% to 10%. In practice, both the detection rate and false-positive rate increase with age, thus detection and positive rates will vary depending on the age distribution of the screening population.

**Reference Values:**

**DOWN SYNDROME**
Calculated screen risks <1/230 are reported as screen negative.
Risks ≥ 1/230 are reported as screen positive.

**TRISOMY 18**
Calculated screen risks <1/100 are reported as screen negative.
Risks ≥ 1/100 are reported as screen positive. A numeric risk for trisomy 18 risk is provided with positive results on non-diabetic, non-twin pregnancies.

An interpretive report will be provided.

**Clinical References:**
Fish and Shellfish Panel IgG

Reference Values:
Clam IgG
Codfish/Scrod IgG
Crab IgG
Lobster IgG
Oyster IgG
Red Snapper IgG
Salmon IgG
Sardine/Pilchard IgG
Shrimp IgG
Sole IgG
Trout IgG
Tuna IgG

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Flecainide, Serum

Clinical Information: Flecainide (Tambocor) is a class I cardiac antiarrhythmic agent with electrophysiologic properties similar to lidocaine, quinidine, procainamide, and tocainide. Flecainide produces a dose-related decrease in intracardiac conduction in all parts of the heart, with the greatest effect on the His-Purkinje system. Atrial effects are limited. Flecainide causes a dose-related and plasma concentration-related decrease in single and multiple premature ventricular contractions and can suppress recurrence of ventricular tachycardia. Flecainide is eliminated from blood by hepatic metabolism as well as renal clearance; significant changes in either organ system will cause impaired clearance. During preclinical trials, patients with congestive heart failure were observed to have radically altered clearance properties. Cardiac toxicity attributed to flecainide is related to its cardiac conduction slowing properties. Excessive prolongation of PR, QRS, and QT intervals occurs with increased amplitude of the T wave. Reductions in myocardial rate, contractility, as well as conduction disturbances, are also associated with excessive dose and plasma concentration of flecainide. Death can occur from hypotension, respiratory failure, and asystole. Flecainide is contraindicated in patients with sick sinus syndrome. It causes sinus bradycardia, sinus pause, or sinus arrest.

Useful For: Optimizing dosage Assessing toxicity Monitoring compliance

Interpretation: Flecainide is most effective in premature ventricular contractions suppression at plasma concentrations in the range of 0.2 to 1.0 mcg/mL. Plasma concentrations >1.0 mcg/mL are associated with a high rate of cardiac adverse experiences such as conduction defects or bradycardia. Therapeutic concentration: 0.2 to 1.0 mcg/mL. Toxic concentration: >1.0 mcg/mL

Reference Values:
**FLG**

**FLG Gene, Mutation Analysis**

**Clinical Information:** Ichthyosis vulgaris is a common disease with an incidence rate of approximately 1 in 250. It is characterized by palm hyperlinearity, keratosis pilaris, xerosis, and prominent fine scaling of the extensor surfaces of the extremities, the scalp, central part of the face, and the trunk. The clinical onset typically occurs within the first few years of life. Approximately 37% to 50% of people with ichthyosis vulgaris have atopic diseases and about 8% of patients with atopic diseases have classic features of ichthyosis vulgaris. A large number of epidemiological studies support an increased risk and severity of asthma that occurs in association with atopic disease. Clinical presentation associated with ichthyosis vulgaris can be confirmed by genetic testing. Ichthyosis vulgaris is caused by loss-of-function alterations in the filaggrin (FLG) gene on chromosome 1q21. Filaggrin is a filament aggregating protein that promotes terminal differentiation of the epidermis and skin barrier formation. This prevents epidermal water loss and inhibits entry of allergens, toxic chemicals, and infectious organisms. Loss of filaggrin expression causes cytoskeletal disorganization leading to clinical phenotype associated with ichthyosis vulgaris. FLG mutations are found in about 7.7% of Europeans and 3% of Asians. However, these mutations appear to be less common in dark-skinned ethnicities. The R501X and 2282del4 are complete loss-of-function mutations accounting for approximately 80% of mutations in the Northern European population. However, they are rarer in the Southern European population. These 2 alterations have been shown to be very strong predisposing factors for atopic diseases. FLG mutations in other ethnicities are different than those found in European-origin populations. This disease is inherited in a semidominant manner (ie, heterozygotes have either no symptoms or milder ichthyosis vulgaris and homozygotes/compound heterozygotes show marked ichthyosis vulgaris).

**Useful For:** Genetic diagnosis of ichthyosis vulgaris for clinical management, risk assessment for atopic diseases and atopic disease-associated asthma, and genetic counseling for family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
Interpretive report will be provided.


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**FLNDR**

**Flounder (Bothidae/Pleuronectidae Fam) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
**FLT 19739**

**FLT3 Mutation Analysis, Varies**

**Clinical Information:** The FMS-like tyrosine gene (FLT3) codes for a transmembrane receptor/signaling protein (FLT3) of the tyrosine kinase group. Binding of FLT3 ligand to the FLT3 receptor ultimately leads to production of proteins that cause cell growth and inhibit cell death through apoptosis. Recently, mutations in FLT3 have been found in some hematopoietic neoplasms, and are particularly common in adult acute myeloid leukemia (AML) with an overall incidence of approximately 20% to 30%. The highest mutation rates are seen in adult patients with AML and normal- or intermediate-risk cytogenetics, and patients with acute promyelocytic leukemia. The most common FLT3 mutation consists of internal tandem duplication (ITD) of DNA sequences found in exons 14 or 15. In some subgroups of adults with AML, the presence of an FLT3 ITD mutation has been found to be an adverse prognostic indicator. The second most common mutation is a point mutation in the codon for an aspartate residue (D835) that resides in the activation loop of the FLT3 protein. D835 mutations have been identified in approximately 7% of AML cases, but, at this time, it is not clear if the presence of this mutation has any prognostic significance. It is thought that both types of FLT3 mutations lead to constitutive (always present, independent of internal or external stimuli) FLT3 activation. Identification of an FLT3 mutation in AML is clinically useful not only because of the prognostic information it provides, but also because FLT3-inhibitory drugs have shown promise as useful therapeutic agents.

**Useful For:** A prognostic indicator in some acute myeloid leukemia patients

**Interpretation:** An interpretive report will be issued indicating whether the FLT3 internal tandem duplication or D835 mutation, or both, was detected. Mutation status will be indicated as positive or negative.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


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**FFLRO 91795**

**Flunitrazepam Confirmation, Serum**

**Reference Values:**

<table>
<thead>
<tr>
<th>Units</th>
<th>Flunitrazepam ng/mL</th>
<th>7-Aminoflunitrazepam ng/mL</th>
</tr>
</thead>
</table>

Peak plasma Flunitrazepam concentrations in patients receiving chronic, recommended dosages: 10 – 20 ng/mL.

Note: Flunitrazepam is not legally marketed in the United States.

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**FL 8641**

**Fluoride, Plasma**

**Clinical Information:** Fluoride induces bone formation by stimulating osteoblasts. Because fluorides increase bone density, they are used in dental preparations and as an antosteoporotic agent. However, prolonged high exposure to fluoride produces changes in bone morphology consistent with osteomalacia, including prolonged mineralization lag time and increased osteoid thickness. The adverse skeletal effects of fluoride are associated with plasma fluoride >4 mcmol/L. Chronic fluorosis may produce osteosclerosis, periostitis, calcification of ligaments and tendons, and crippling deformities. Prolonged exposure to the fluoride-containing antifungal agent voriconazole can produce high plasma fluoride concentrations and bone changes (periostitis).
**Useful For:** Assessing accidental fluoride ingestion Monitoring patients receiving sodium fluoride for bone disease or patients receiving voriconazole therapy

**Interpretation:** Humans exposed to fluoride-treated water typically have plasma fluoride in the range of 1 to 4 mcmol/L. Those who are not drinking fluoride-treated water have plasma fluoride <1 mcmol/L. Plasma fluoride values >4 mcmol/L indicate excessive exposure and are associated with periostitis.

**Reference Values:** 0.0-4.0 mcmol/L


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**Fluoropyrimidine Drug (5-FU) Sensitivity Genotyping, Blood**

**Clinical Information:** 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydrorpyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation. This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity. Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment. In addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation. The thymidine synthase (TYMS) enzyme catalyzes the transformation of deoxouridine monophosphate (dUMP) to thymidine monophosphate (dTMP), essential for DNA replication, and is the main intracellular target of fluoropyrimidines. The promoter region of the thymidine synthase gene (TYMS) is polymorphic, containing both a 28-base pair tandem repeat and a single nucleotide polymorphism (table 1), each of which have been shown to influence the translation efficiency of TYMS mRNA. These variations may be associated with fluoropyrimidine toxicity and tumor response, although the literature is mixed in this regard. The repeat is usually 2 or 3 28-base pair segments long (noted as 2R and 3R respectively) with 3R being considered wild type; and the single nucleotide polymorphism (SNP) occurs in the 12th base of the second repeat, when a 3R allele is present, and is noted as 3RG (wild type) or 3RC (when the SNP is present).

<table>
<thead>
<tr>
<th>Gene</th>
<th>cDNA Numbering</th>
<th>Alternative Name</th>
<th>Enzyme Activity</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPYD</td>
<td>c.1905+1G-&gt;A</td>
<td>*1</td>
<td>High risk for fluoropyrimidine toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.1679T-&gt;G</td>
<td>*4</td>
<td>Normal activity</td>
<td></td>
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<tr>
<td></td>
<td>c.2983G-&gt;T</td>
<td>*10</td>
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<tr>
<td></td>
<td>c.1003G-&gt;T</td>
<td>*11</td>
<td>Normal activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.62G-&gt;A</td>
<td>*8</td>
<td>High risk for fluoropyrimidine toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.1156G-&gt;T</td>
<td>*9B</td>
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<tr>
<td></td>
<td>c.557A-&gt;G</td>
<td>*9A</td>
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<tr>
<td></td>
<td>rs115232898</td>
<td>*3</td>
<td>Normal activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs183205964</td>
<td>*4</td>
<td>Normal activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs1601C-&gt;T</td>
<td>*5</td>
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<td></td>
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<td>rs2853542</td>
<td>*7</td>
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<td></td>
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<td>rs86G-&gt;C</td>
<td>*8</td>
<td>Normal activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs2853542</td>
<td>*9</td>
<td>Normal activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs183205964</td>
<td>*10</td>
<td>Normal activity</td>
<td></td>
</tr>
</tbody>
</table>

**Useful For:** Identifying individuals at increased risk of toxicity when considering 5-fluorouracil (5-FU) and capcitabine chemotherapy treatment Variations detected in the DPYD gene are also associated with dihydropyrimidine dehydrogenase (DPD) deficiency (OMIM 274270)
Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:
3. FDA Table of Pharmacogenomic Biomarkers in Drug Labeling. Available at:
   http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Fluoropyrimidine Drug (5-FU) Sensitivity Genotyping, Saliva

Clinical Information: 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation.(1,2) Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment.(3) In addition, pathogenic homozygous or compound heterozygous variants within DPYD are also associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation. The thymidine synthase (TYMS) enzyme catalyzes the transformation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP), essential for DNA replication, and is the main intracellular target of fluoropyrimidines. The promoter region of the thymidine synthase gene (TYMS) is polymorphic, containing both a 28-base pair tandem repeat and a single nucleotide polymorphism (table 1), each of which have been shown to influence the translation efficiency of TYMS mRNA. These variations may be associated with fluoropyrimidine toxicity and tumor response, although the literature is mixed in this regard.(4) The repeat is usually 2 or 3 28-base pair segments long (noted as 2R and 3R respectively) with 3R being considered wild type; the single nucleotide polymorphism (SNP) occurs in the 12th base of the second repeat, when a 3R allele is present, and is noted as 3RG (wild type) or 3RC (when the SNP is present). Table 1. Known Genetic Variations Associated with Fluoropyrimidine Treatment Gene cDNA numbering Alternative Name Enzyme Activity Phenotype* DPYD No Variations Identified *1 c.1905+1G->A *2A No activity or significantly reduced activity High risk for fluoropyrimidine toxicity c.1679T->G *13 c.2846A->T rs67376798 c.1129-5923C->G rs75017182 c.1898delC *3 Probable reduced function Increased risk for fluoropyrimidine toxicity c.299_302del *7 c.703C->T *8 c.85T->C and c.2656C->T *9B c.2983G->T *10 c.1003G->T *11 c.62G->A and c.1156G->T *12 c.557A->G rs115232898 c.1601C->T *4 Normal activity Normal risk for fluoropyrimidine toxicity c.1627A->G *5 c.2194C->T *6 c.85T->C *9A TYMS No Variation Identified 3RG c.-58_-31del28 2R Decreased expression Increased risk for toxicity Possible improved tumor response c.-58G->C rs2853542 c.-86G->C rs183205964 * Other or novel variations, besides those listed here, may also impact fluoropyrimidine related side effects and tumor response. The DPYD gene is located on chromosome 1 and contains 2 transcripts. The longest transcript (NM_000110.3) contains 23
exons, and the shortest transcript (NM_001160301.1) contains 6 exons, with exon 6 being unique to this transcript. All exons (total of 24 from both transcripts), and exon-intron boundaries are assessed. The TYMS gene is located on chromosome 18 and contains 7 exons (transcript NM_001071.2). The 5’ UTR region is assessed. Genetic variations involved in the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes including toxicity and tumor response.

**Useful For:** Identifying individuals at increased risk of toxicity when considering 5-fluorouracil (5-FU) and capecitabine chemotherapy treatment. Variations detected in the DPYD gene are also associated with dihydropyrimidine dehydrogenase (DPD) deficiency (OMIM 274270).

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FLUOX 80228**

**Fluoxetine, Serum**

**Clinical Information:** Fluoxetine is a selective serotonin reuptake inhibitor approved for treatment of bulimia, obsessive-compulsive behavior, panic, premenstrual dysphoria, and major depressive disorder, with a variety of off-label uses. Both fluoxetine and its major metabolite, norfluoxetine, are pharmacologically active, and are reported together in this assay. Most individuals respond optimally when combined serum concentrations for both parent and metabolite are in the therapeutic range (120-300 ng/mL) at steady state. Due to the long half-lives of parent and metabolite (1-6 days), it may take several weeks for patients to reach steady-state concentrations. Fluoxetine is a potent inhibitor of the metabolic enzyme CYP2D6, with lesser inhibitory effects on CYP2C19 and CYP3A. Therapy with fluoxetine is therefore subject to numerous drug interactions, which is compounded by wide interindividual variability in fluoxetine pharmacokinetics. Measurement of the drug is useful for managing comedinations, dose or formulation changes, and in assessing compliance. Side effects are milder for fluoxetine than for older antidepressants such as the tricyclics. The most common side effects of fluoxetine therapy include nausea, nervousness, anxiety, insomnia, and drowsiness. Anticholinergic and cardiovascular side effects are markedly reduced compared to tricyclic antidepressants. Fatalities from fluoxetine overdose are extremely rare.

**Useful For:** Monitoring serum concentration of fluoxetine during therapy, Evaluating potential toxicity, Evaluating patient compliance.

**Interpretation:** Most individuals display optimal response to fluoxetine when combined serum levels of fluoxetine and norfluoxetine are between 120 and 300 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. A toxic range has not been well established.

**Reference Values:**
Fluoxetine + norfluoxetine: 120-300 ng/mL


**PROLX**

Fluphenazine (Prolixin), Serum

**Reference Values:**
Reference Range: 1.0 - 10 ng/mL

**FFLUR**

Flurazepam (Dalmane) and Desalkylflurazepam

**Reference Values:**
Flurazepam:
Reference Range: 0 - 30 ng/mL

Desalkylflurazepam:
Reference Range: 30 - 150 ng/mL

Flurazepam + Desalkylflurazepam:
Reference Range: 30 - 180 ng/mL

**17BFP**

Fluticasone 17-Beta-Carboxylic Acid, Urine

**Clinical Information:** Inhaled corticosteroids are the single most effective therapy for adult patients with asthma. Even low doses of inhaled corticosteroids have been shown to reduce mortality related to asthma. The September 2007 issue of Pediatrics reported that "Verification of (asthma) treatment adherence by objective measures remains necessary."(1) In this pediatric asthma adherence study, the 104 asthmatic children and their parents grossly overestimated their medication adherence. Over 1 of 3 responses reported full compliance to medications when no medications had been taken. Over 46% of individuals exaggerated their adherence by at least 25%. The authors concluded that "Under the best of conditions in this study, accuracy of self-report was insufficient to provide a stand-alone measure of adherence."(1,2) Fluticasone propionate (FP) is an inhaled corticosteroid with anti-inflammatory and immunosuppressive properties commonly used for the treatment of asthma, airway inflammation, and allergic rhinitis. FP is typically well tolerated and has a low risk for adverse systemic effects when utilized at recommended therapeutic doses. However, noncompliance with recommended FP therapy may result in poorly controlled asthma or misinterpretation of the patient's therapeutic responsiveness. Patients with excessive exposure to FP may present with clinical features of Cushing syndrome, but with evidence of hypothalamus-pituitary-adrenal axis suppression, including suppressed cortisol levels. Conversely, a patient not administering the drug as recommended may have their therapeutic responsiveness interpreted, in error by the patient or clinician, as steroid-resistance. FP has low oral bioavailability and high hepatic first-pass metabolism, which results in low plasma FP concentrations; any systemic levels are believed to occur through adsorption from the lungs. Native FP absorbed by the gastrointestinal tract (<1% total FP) is rapidly metabolized by cytochrome P450 isoform 3A4 to yield fluticasone 17-beta-carboxylic acid, its primary metabolic product.(3) Fluticasone 17-beta-carboxylic acid is pharmacologically inactive and has increased water solubility such that it is excreted in urine. Accordingly, fluticasone 17-beta-carboxylic acid is detected in urine in individuals recently exposed to inhaled FP therapy. Fluticasone 17-beta-carboxylic acid may be detected in urine as early as 16 to 24 hours following a patient's first administration of low dose (220 mcg) FP therapy. The window of detection for fluticasone 17-beta-carboxylic acid is 6 days following cessation of FP therapy.

**Useful For:** Assessing compliance (recent exposure) to fluticasone propionate therapy An aid in the evaluation of secondary adrenal insufficiency
**Interpretation:** Elevated fluticasone 17-beta-carboxylic acid indicates recent exposure to fluticasone propionate (FP). Fluticasone 17-beta carboxylic acid concentration <10 pg/mL indicates that the patient may not have administered inhaled FP therapy within the preceding 6 days. Validated concerns about suboptimal patient adherence to asthma controller medications should lead to patient and provider interactions to address potential compliance issues.

**Reference Values:**
Negative
Cutoff concentration: 10 pg/mL

Values for normal patients not taking fluticasone propionate should be less than the cutoff concentration (detection limit).

**Clinical References:**

**FFVOX 57731**

**Fluvoxamine (Luvox)**

**Reference Values:**
Units: ng/mL

Expected fluvoxamine concentrations on recommended daily dosage regimens:
50 – 900 ng/mL

**FOL 9198**

**Folate, Serum**

**Clinical Information:** The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate. Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characterized by macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions. Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

**Useful For:** Investigation of suspected folate deficiency

**Interpretation:** Serum folate is a relatively nonspecific test. Low serum folate levels may be seen in the absence of deficiency and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results <4 mcg/L are suggestive of folate deficiency. The cutoff is based on consensus and was derived from the US NHANES III data.
Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Serum folate measurement is preferred over RBC folate measurement due to considerable analytic variability (coefficient of variation: CV) of assays. Both results give the same interpretation (internal Mayo study) therefore RBC folate quantitation is not recommended. Additional serum testing with homocysteine and methylmalonic acid (MMA) determinations may help distinguish between vitamin B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, the analytic variability (CV) of both serum and RBC folate assays is considerable. Homocysteine and MMA levels are alternate determinates of folate deficiency. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:

> or =4.0 mcg/L
<4.0 mcg/L suggests folate deficiency


Follicle-Stimulating Hormone (FSH), Serum

Clinical Information: Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. The menstrual cycle is divided by a midcycle surge of both FSH and LH into a follicular phase and a luteal phase. FSH appears to control gametogenesis in both males and females.

Useful For: An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

Interpretation: In both males and females, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. FSH and LH are generally elevated in: -Primary gonadal failure -Complete testicular feminization syndrome -Precocious puberty (either idiopathic or secondary to a central nervous system lesion) -Menopause (postmenopausal FSH levels are generally >40 IU/L) -Primary ovarian hypofunction in females -Primary hypogonadism in males Normal or decreased FSH in: -Polycystic ovary disease in females FSH and LH are both decreased in failure of the pituitary or hypothalamus.

Reference Values:

Males
1-7 days: < or =3.0 IU/L
8-14 days: < or =1.4 IU/L
15 days-3 years: < or =2.5 IU/L
4-6 years: < or =6.7 IU/L
7-8 years: < or =4.1 IU/L
9-10 years: < or =4.5 IU/L
11 years: 0.4-8.9 IU/L
12 years: 0.5-10.5 IU/L
13 years: 0.7-10.8 IU/L
14 years: 0.5-10.5 IU/L
15 years: 0.4-18.5 IU/L
16 years: < or =9.7 IU/L
17 years: 2.2-12.3 IU/L
> or =18 years: 1.0-18.0 IU/L
TANNER STAGES*
Stage I: < or = 3.7 IU/L
Stage II: < or = 12.2 IU/L
Stage III: < or = 17.4 IU/L
Stage IV: 0.3-8.2 IU/L
Stage V: 1.1-12.9 IU/L

*Puberty onset occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females
1-7 days: < or = 3.4 IU/L
8-14 days: < or = 1.0 IU/L
15 days-6 years: < or = 3.3 IU/L
7-8 years: < or = 11.1 IU/L
9-10 years: 0.4-6.9 IU/L
11 years: 0.4-9.0 IU/L
12 years: 1.0-17.2 IU/L
13 years: 1.8-9.9 IU/L
14-16 years: 0.9-12.4 IU/L
17 years: 1.2-9.6 IU/L
> or = 18 years:
  Premenopausal
    Follicular: 3.9-8.8 IU/L
    Midcycle: 4.5-22.5 IU/L
    Luteal: 1.8-5.1 IU/L
    Postmenopausal: 16.7-113.6 IU/L

TANNER STAGES*
Stage I: 0.4-6.7 IU/L
Stage II: 0.5-8.7 IU/L
Stage III: 1.2-11.4 IU/L
Stage IV: 0.7-12.8 IU/L
Stage V: 1.0-11.6 IU/L

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.


antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*

allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FFPG4 Food Panel IgG4 (532) Reference Values:**

- Corn IgG4
- Egg White IgG4
- Egg Yolk IgG4
- Milk Cow IgG4
- Peanut IgG4
- Soybean IgG4
- Wheat IgG4
- Yeast (Saccharomyces cerevisiae) IgG4

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question.

**FFPII Food Panel II IgG Reference Values:**

- Barley IgG <2.0
The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FOOD2**

**Food-Fruit Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FOOD2**

**Food-Fruit Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Food-Grain Panel

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Food-Meat Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3.50-17.4</td>
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<td>4</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Food-Nut Panel # 1**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


Food-Seashore Panel

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.

**FOOD3 81871**

**Food-Vegetable Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**FRMH 82869**

**Formaldehyde, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
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**FFOAB 90299**

**Formic Acid, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

Normal: Average 5 mcg/mL (range 0-12)

Formic acid is a metabolite of Formaldehyde and an index of exposure to Formaldehyde and (other) precursors.

**FFRM 90298**

**Formic Acid, Urine**

**Reference Values:** Reporting limit determined each analysis

Creatinine (mg/L)

U.S. Population (10th â€“ 90th percentiles, median)

All participants:
FOXL2

**FOXL2, Granulosa Cell Tumor, c.402C->G Mutation Analysis**

**Clinical Information:** Granulosa cell tumor (GCT) represents approximately 5% to 10% of all ovarian malignancies and is the most common type of malignant ovarian sex-cord stromal tumor. The majority of patients with GCT (95%) are adults and 5% are juveniles. The histopathological diagnosis of GCT is challenging. Forkhead box L2 (FOXL2) gene is involved in ovarian development and function. The FOXL2 gene point mutation 402C->G in exon 1 (C134W) was reported in the majority of adult GCT (>90%), 5% to 10% of thecomas (tumors closely related to GCT) and <10% of juvenile GCT cases, but not in other ovarian tumors. Detection of FOXL2 mutation aids in the clinical diagnosis of adult GCT.

**Useful For:** Aiding in the diagnosis of adult granulosa cell tumor

**Interpretation:** The presence of forkhead box L2 (FOXL2) mutation 402C->G supports the diagnosis of granulosa cell tumor (GCT), but does not rule out the diagnosis of ovarian thecomas (5%-10%). The presence of wild-type FOXL2 does not rule out the diagnosis of GCT.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

FMIL

**Foxtail Millet, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
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Fragile X Syndrome, Molecular Analysis

Clinical Information: Fragile X syndrome is an X-linked disorder with variable expression in males and females. It is caused by an expansion of the CGG trinucleotide repeat in the FMR1 gene, located on the X chromosome. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 5 to 44. These normal alleles are passed from generation to generation with the number of repeats remaining constant. Small expansions, called premutations, most often range from 59 to 200 CGG repeats. Premutation carriers do not exhibit features of fragile X syndrome, but are at risk for other FMR1-related disorders such as fragile X tremor/ataxia syndrome (FXTAS) and premature ovarian failure (POF). Transmission of a premutation by a male to his daughter usually results in little or no change in the CGG repeat number. Transmission of a premutation by a female to her son or daughter usually results in further expansion, either to a larger premutation or a full mutation. The risk for a female premutation carrier to have a child affected with fragile X syndrome by expansion to a full mutation increases with the number of CGG repeats in the premutation. Full mutations can be 200 to thousands of repeats long, and are associated with abnormal methylation of a region adjacent to the FMR1 gene. This is thought to interfere with normal FMR1 gene expression, resulting in fragile X syndrome. There are multiple clinical phenotypes associated with expansion (premutations and full mutations) in the FMR1 gene. Fragile X Syndrome: Approximately 1/4000 individuals (male and female) are affected with fragile X syndrome. Most affected males exhibit moderate mental retardation, with affected females having milder (if any) cognitive deficiency. Neuropsychiatric diagnoses such as autism spectrum and anxiety disorders are common. Characteristic physical features include a long face with prominent jaw, protruding ears, connective tissue abnormalities, and large testicles in postpubertal males. Fragile X Tremor/Ataxia Syndrome (FXTAS): FXTAS is a neurodegenerative disorder that is clinically distinct from fragile X syndrome. Both male and female premutation carriers are at risk for FXTAS. However, the disorder is much less common, milder in presentation, and shows a later age of onset in females. Clinical hallmarks of the disorder include intention tremor, gait ataxia, dementia, and neuropsychiatric symptoms. The risk...
for FXTAS increases as the number of CGG repeats increases, and the majority of individuals with FXTAS have CGG repeat expansions of 70 or more. Penetrance of clinical symptoms is associated with increasing age, with the majority of affected males showing symptoms between age 70 and 90. Premature Ovarian Failure (POF): Female premutation carriers are at risk for increased follicular stimulating hormone (FSH) levels, early menopause, and POF. Penetrance and early onset of female reproductive symptoms correlates with increasing size of the CGG repeat, and reaches its highest penetrance at approximately 80 to 90 repeats. Of note, penetrance actually remains stable or may even decrease at approximately 100 repeats. There is no risk for increased penetrance of the POF phenotype due to maternal or paternal inheritance of the expanded CGG repeat.

**Useful For:** Determination of carrier status for individuals with a family history of fragile X syndrome or X-linked mental retardation. Confirmation of a diagnosis of fragile X syndrome, fragile X tremor/ataxia syndrome, or premature ovarian failure caused by expansions in the FMR1 gene. Prenatal diagnosis of fragile X syndrome when there is a documented FMR1 expansion in the family.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
- Normal alleles: 5-44 CGG repeats
- Intermediate (grey zone) alleles: 45-54 CGG repeats
- Premutation alleles: 55-200 CGG repeats
- Full mutation alleles: >200 CGG repeats

**Clinical References:**

---

**Francisella Tularensis Antibody**

**Reference Values:**
Reference Range: <1:20

- Interpretive Criteria:
  - <1:20 Negative
  - 1:20 - 1:80 Equivocal
  - > or =1:160 Positive

In the presence of compatible symptoms, a Francisella tularensis antibody titer of 1:160 or greater in an acute specimen supports a presumptive diagnosis of tularemia. However, a titer > or =1:160 may also reflect past infection. An equivocal titer may be due to crossreactive antibodies (Brucella, Yersinia, or Proteus OX19), past infection, or very recent infection. A four-fold rise in titer between acute and convalescent sera is required for definitive serologic diagnosis of tularemia.

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**Free Fatty Acids, Total, Serum**

**Clinical Information:** All but 2% to 5% of serum fatty acids are esterified. The "nonesterified" or "free" fatty acids are protein-bound. The amount of free fatty acids in the serum rises after a fatty meal, but tends to fall after ordinary meals. Levels are elevated in obesity. Lipoactive hormones such as epinephrine, norepinephrine, glucagon, thyrotropin, and adrenocorticotropic release free fatty acids. Tumors producing such hormones cause release of excessive quantities of free fatty acids. Serum free fatty acids are also increased in patients with uncontrolled type 2 diabetes mellitus and are an indicator of insulin resistance. Free fatty acids are associated with increased reactive oxygen species (ROS), probably mediated by free fatty acid activation of NADPH oxidase. The link between increased ROS and decreased...
nitric oxide production is a contributor to endothelial dysfunction.

**Useful For:** Evaluation of metabolic status of persons with endocrinopathies Detection of pheochromocytoma and of glucagon-, thyrotropin-, and adrenocorticotropin-secreting tumors Monitoring of control of diabetes mellitus (serum-free glycerol is a very useful companion test in assessing diabetes and may be ordered by special request from Mayo Medical Laboratories). The correlation with insulin resistance and downstream cardiovascular risk may be a useful treatment aid in some patients.

**Interpretation:** Abnormally high levels of free fatty acids are associated with uncontrolled diabetes mellitus and with conditions that involve excessive release of a lipoactive hormone such as epinephrine, norepinephrine, glucagon, thyrotropin, and adrenocorticotropin.

**Reference Values:**

> or =16 years: 0.00-0.72 mmol/L
Reference values have not been established for patients who are <16 years of age.


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**Free Thyroxine Index (FTI), Serum**

**Clinical Information:** The determination of the total thyroxine (T4) concentration is of importance in laboratory diagnostics for differentiating between euthyroid, hyperthyroid, and hypothyroid conditions. As the major fraction of the total thyroxine is bound to transport proteins (thyroxine-binding globulin: TBG, prealbumin, and albumin), the determination of total T4 only provides correct information when the thyroxine-binding capacity in serum is normal. The free thyroid hormones are in equilibrium with the hormones bound to the carrier proteins. The thyroid binding capacity or T-uptake assay provides a measure of the available thyroxine-binding sites. Determination of the free thyroxine index (FTI) from the quotient of total T4 and thyroxine-binding index (TBI) (TBI=result of the T-uptake determination) takes into account changes in the thyroid hormone carrier proteins and the thyroxine level. While total T4 is a relatively reliable indicator of T4 levels in the presence of normal binding proteins, it is not a reliable indicator when binding proteins are abnormal. For example, increases in thyroxine-binding proteins may cause increased total T4 levels despite normal free T4 levels and normal thyroid function. Results are changed by drugs or physical conditions that alter the patient's TBG levels, or drugs that compete with endogenous T4 and T3 for protein-binding sites. Direct measurement of free thyroxine (FRT4 / T4 [Thyroxine], Free, Serum by immunoassay) has replaced the FTI test in most clinical situations.

**Useful For:** Estimating the amount of circulating free thyroxine (free thyroxine index) using the total thyroxine and thyroid binding capacity (T-uptake)

**Interpretation:** The free thyroxine index (FTI) is determined by the following calculation: FTI = Thyroxine (T4)/Thyroid Binding Capacity The FTI is a normalized determination that remains relatively constant in healthy individuals and compensates for abnormal levels of binding proteins. Hyperthyroidism causes increased FTI and hypothyroidism causes decreased values.

**Reference Values:**

Thyroxine Binding Capacity (units are in Thyroxine Binding Index [TBI]):

0-19 years: 0.8-1.2 TBI

> or =20 years: 0.8-1.3 TBI

T4 Total (T4):

0-5 days: 5.0-18.5 mcg/dL
6 days-2 months: 5.4-17.0 mcg/dL
3-11 months: 5.7-16.0 mcg/dL
1-5 years: 6.0-14.7 mcg/dL
6-10 years: 6.0-13.8 mcg/dL
11-19 years: 5.9-13.2 mcg/dL

> or =20 years: 4.5-11.7 mcg/dL
Free Thyroxine Index:
0-5 days: 5.1-20.8 mcg/dL
6 days-2 months: 5.5-18.0 mcg/dL
3-11 months: 5.7-16.8 mcg/dL
1-5 years: 5.9-15.0 mcg/dL
6-10 years: 6.0-13.9 mcg/dL
11-19 years: 5.9-13.2 mcg/dL
> or =20 years: 4.8-12.7 mcg/dL


**Friedreich Ataxia Repeat Expansion Analysis - Unknown Mutation**

Reference Values:
A final report will be attached in MayoAccess.

**Friedreich Ataxia, Frataxin, Quantitative, Blood Spot**

Clinical Information: Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 Caucasians. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Hypertrophic cardiomyopathy is present in approximately two-thirds of patients with FA and represents the most frequent cause of premature death. Most individuals begin experiencing initial symptoms between 10 and 15 years of age, although there are atypical late-onset forms with initial symptoms presenting after age 25. FA is caused by mutations in the FXN gene encoding a mitochondrial protein, frataxin. Mutations in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 98% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of the FXN gene. The remaining 2% of FA patients have the trinucleotide expansion on 1 allele and a point mutation or deletion on the second allele. Normal alleles contain between 5 and 33 GAA repeats. Disease-causing alleles typically range from 66 to 1,700 repeats, though the majority of individuals with FA have repeats ranging from 600 to 1,200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. However, a molecular-based analysis is not able to effectively monitor treatment, is not amenable to multiplexing with other disease analytes, nor can it be efficiently utilized for population screening. In contrast, a protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA.

Useful For: Diagnosing individuals with Friedreich ataxia Monitoring frataxin levels in patients with Friedreich ataxia

Interpretation: Normal results (> or =15 ng/mL for pediatric and > or =21 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

Reference Values:
Pediatric (<18 years) normal frataxin: > or =15 ng/mL
Adults (> or =18 years) normal frataxin: > or =21 ng/mL

**Friedreich Ataxia, Frataxin, Quantitative, Whole Blood**

**Clinical Information:** Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 Caucasians. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Hypertrophic cardiomyopathy is present in approximately two-thirds of patients with FA and represents the most frequent cause of premature death. Most individuals begin experiencing initial symptoms between 10 and 15 years of age, although there are atypical late-onset forms with initial symptoms presenting after age 25. FA is caused by mutations in the FXN gene encoding a mitochondrial protein, frataxin. Mutations in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 98% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of the FXN gene. The remaining 2% of FA patients have the trinucleotide expansion on 1 allele and a point mutation or deletion on the second allele. Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1,700 repeats, though the majority of individuals with FA have repeats ranging from 600 to 1,200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. However, a molecular-based analysis is not able to effectively monitor treatment, is not amenable to multiplexing with other disease analytes, nor can it be efficiently utilized for population screening. In contrast, a protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA.

**Useful For:** Diagnosing individuals with Friedreich ataxia Monitoring frataxin levels in patients with Friedreich ataxia

**Interpretation:** Normal results (> or =19 ng/mL for pediatric and > or =21 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

**Reference Values:**
- Pediatric (<18 years) normal frataxin: > or =19 ng/mL
- Adults (> or =18 years) normal frataxin: > or =21 ng/mL

**Clinical References:**

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**Fructosamine, Serum**

**Clinical Information:** Fructosamine is a general term, which applies to any glycated protein. It is formed by the nonenzymatic reaction of glucose with the a- and e-amino groups of proteins to form intermediate compounds called aldimines. These aldimines may dissociate or undergo an Amadori rearrangement to form stable ketoamines called fructosamines. This nonenzymatic glycation of specific proteins in vivo is proportional to the prevailing glucose concentration during the lifetime of the protein. Therefore, glycated protein measurement in the diabetic patient is felt to be a better monitor of long-term glycemic control than individual or sporadic glucose determinations. The best known of these proteins is glycated hemoglobin which is often measured as hemoglobin A1c, and reflects glycemic control over the past 6 to 8 weeks. In recognition of the need for a measurement that reflects intermediate-term glycemic control and was easily automated, a nonspecific test, termed fructosamine, was developed. Since albumin is the most abundant serum protein, it accounts for 80% of the glycated serum proteins, and thus, a high proportion of the fructosamine. Although a large portion of the color generated in the reaction is contributed by glycated albumin, the method will measure all proteins, each with a different half-life and...
different levels of glycation.

**Useful For:** Assessing intermediate-term glycemic control

**Interpretation:** In general, fructosamine reflects glycemic control in diabetic patients over the previous 2 to 3 weeks. High values indicate poor control.

**Reference Values:**
200-285 mcmol/L


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**Fructose, Semen or Seminal Plasma**

**Clinical Information:** Fructose is produced in the male reproductive tract by the seminal vesicles and is released into the semen during ejaculation. Fructose is the energy source for sperm motility.

**Useful For:** Fructose testing should be considered for patients with azoospermia and low volume ejaculates to establish the origin of the azoospermia.

**Interpretation:** A positive (indicated by color change) fructose is considered normal. A semen specimen that contains no sperm (azoospermia) and is fructose negative may indicate an absence of the seminal vesicles, absence of the vas deferens in the area of the seminal vesicles, or an obstruction at the level of the seminal vesicles.

**Reference Values:**
Positive


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**Fruit Panel IgG**

**Reference Values:**

<table>
<thead>
<tr>
<th>Fruit</th>
<th>IgG Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Apricot</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Banana</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Blueberry</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Cranberry</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Grape</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Orange</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Papaya</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Peach</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Pear</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Pineapple</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Plum</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Raspberry</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Strawberry</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
</tbody>
</table>

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.
This test should only be ordered by physicians who recognize the limitations of the test.

**FTCD Gene, Full Gene Analysis**

**Clinical Information:** Glutamate formiminotransferase deficiency is an autosomal recessive inborn error of folate and histidine metabolism caused by a deficiency of the enzyme, glutamate formiminotransferase-cyclodeaminase, which is encoded at the FTCD loci on chromosome 21q22.3. Glutamate formiminotransferase deficiency presents as a clinical spectrum that ranges from asymptomatic to severe. Individuals with the severe form of disease are reported to have mental and physical retardation and anemia, whereas the mild form is associated with a lesser degree of developmental delay. Of note, the association of the enzyme deficiency with mental retardation has been disputed in the literature. An elevated amount of urine formiminoglutamate (FIGLU) is a cardinal sign of glutamate formiminotransferase deficiency for both the severe and mild clinical phenotypes. However, higher levels of urine FIGLU are observed in patients with milder forms of the disease and these levels occur in the absence of histidine loading; whereas the presence of FIGLU in the urine is typically only observed in severe cases after L-histidine administration. In addition, the severe form of disease is associated with elevated serum folate levels, whereas the milder form of disease is not. As there are discrepancies in FIGLU and serum folate levels among affected individuals, confirmation of suspected cases of glutamate formiminotransferase deficiency may require a liver biopsy for enzymology or the identification of 2 disease-causing mutations in the FTCD gene. Identification of 2 FTCD mutations establishes a molecular diagnosis of glutamate formiminotransferase deficiency, and rules out other diseases associated with high levels of urine FIGLU, such as folate or methylcobalamin deficiencies. Evaluation of the FTCD gene by molecular genetic testing is recommended as a second-tier test subsequent to a positive newborn screen or biochemical test.

**Useful For:** Second-tier test for confirming glutamate formiminotransferase deficiency (indicated by biochemical testing or newborn screening) Ruling out other diseases associated with high levels of urine formiminoglutamate Carrier screening in cases where there is a family history of glutamate formiminotransferase deficiency but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Fungal Culture, Blood**

**Clinical Information:** Due to the high mortality rate from fungemia, the expeditious detection and identification of fungi from the patient's blood can have great diagnostic prognostic importance. Risk factors for fungemia include, but are not limited to, extremes of age, immunosuppression, and those individuals with burns or indwelling intravascular devices.

**Useful For:** Diagnosis and treatment of the etiologic agents of fungemia Select patient population that presents with signs and symptoms of sepsis, especially fever of unknown origin

**Interpretation:** Positive cultures of yeast and filamentous fungi are reported with the organism identification. Positive cultures are usually an indication of infection and are reported as soon as detected.
Correlation of culture results and the clinical situation is required for optimal patient management. A final negative report is issued after 30 days of incubation.

**Reference Values:**
Negative
If positive, notification is made as soon as the positive culture is detected or identified.

**Clinical References:**

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**FDERM**

**87283**

**Fungal Culture, Dermal**

**Clinical Information:** Fungal infections of keratinized tissues (hair, skin, nails) can be caused by dermatophytic fungi belonging to the genera Epidermophyton, Microsporum, and Trichophyton. Opportunistic superficial infections resembling dermatophytoses may be caused by yeasts or by unrelated filamentous fungi that are normally saprobes or plant pathogens. Dermatophytes are usually unable to penetrate deeper tissues. Infection may range from mild to severe.

**Useful For:** Recovery and identification of dermatophyte fungi from hair, skin, and nail infection specimens

**Interpretation:** Positive cultures are reported with organism identification. Negative reports are issued after 30 days incubation.

**Reference Values:**
Negative
If positive, fungus or yeast will be identified.


---

**FGEN**

**84389**

**Fungal Culture, Routine**

**Clinical Information:** Many fungi in the environment cause disease in immunocompromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (eg, persons with AIDS, patients receiving chemotherapy or transplant rejection therapy) has increased. Isolation and identification of the infecting fungus in the clinical laboratory can help guide patient care.

**Useful For:** Diagnosing fungal infections from specimens other than blood, skin, hair, nail, and vagina (separate tests are available for these specimen sites)

**Interpretation:** Positive cultures of yeast and filamentous fungi are reported with the organism identification. The clinician must determine whether or not the presence of an organism is significant. A final negative report is issued after 24 days of incubation.

**Reference Values:**
Negative
If positive, fungus will be identified.

**Fungal Culture, Spinal Fluid**

**Clinical Information:** Many fungi in the environment cause disease in severely compromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (e.g., persons with AIDS, patients receiving chemotherapy, or transplant rejection therapy) has increased. Few fungal diseases can be diagnosed clinically; many are diagnosed by isolating and identifying the infecting fungus in the clinical laboratory.

**Useful For:** Diagnosing fungal infections from cerebrospinal fluid (separate tests are available for other specimen sites)

**Interpretation:** Positive cultures of yeast and filamentous fungi are reported with the organism identification. The clinician must determine whether or not the presence of an organism is significant. A final negative report is issued after 24 days of incubation.

**Reference Values:**
Negative
If positive, fungus will be identified.


---

**Fungal Culture, Vaginal**

**Clinical Information:** Candidal vulvovaginitis is believed to be the most frequent or second most frequent vaginal infection. Depending on the geographical area, its prevalence in women is estimated to be in the range of 5% to 20%. Besides Candida albicans, Candida glabrata, and Candida tropicalis are the most frequently isolated Candida species both from vulvo-vaginitis patients and from healthy carriers.

**Useful For:** Monitoring therapy Managing chronic recurring disease Determining the etiology of infectious vaginitis when other tests have been uninformative

**Interpretation:** Meaningful diagnosis of vaginal candidiasis requires that 1) yeast are demonstrable in the affected area and 2) clinical symptoms and signs are consistent with the disease. Since in up to 20% of healthy women, yeast cells are part of the normal vaginal flora, the presence of Candida on culture may be meaningless or misleading unless other clinical factors are considered.

**Reference Values:**
Negative
If positive, yeast will be identified.


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**Fungal Smear**

**Clinical Information:** Many fungi in the environment cause disease in severely compromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (persons with AIDS, patients receiving chemotherapy or transplant rejection therapy, etc.) has increased. Few fungal diseases can be diagnosed clinically; most are diagnosed by isolating and identifying the infecting fungus in the clinical laboratory.

**Useful For:** Detection of fungi in clinical specimens

**Interpretation:** Positive slides are reported as 1 or more of the following: yeast or hyphae present,
organism resembling Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, or Malassezia furfur.

**Reference Values:**
Negative


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**Fungitell, BAL**

**Clinical Information:** The Fungitell Beta â€“ D Glucan assay detects (1,3) â€“ Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) â€“ Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) â€“ Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) â€“ Beta-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in BAL have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from BAL fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2013) 123:1302-1307).

**Reference Values:**
A reference range for specimens other than serum has not been established.

---

**Fungitell, bronch wash**

**Clinical Information:** The Fungitell Beta â€“ D Glucan assay detects (1,3) â€“ Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) â€“ Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) â€“ Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) â€“ Beta-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in bronchial wash have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from bronchial wash fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2013) 123:1302-1307).

**Reference Values:**
A reference range for specimens other than serum has not been established.

---

**Fungitell, CSF**

**Clinical Information:** The Fungitell Beta â€“ D Glucan assay detects (1,3) â€“ Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as...
the genus Cryptococcus, which produces very low levels of (1,3)-β-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3)-β-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3)-β-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in CSF have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from CSF fluid. Research studies have evaluated the use of the Fungitell assay in CSF during a fungal meningitis outbreak (J. Clin. Microbiol. 2013, 51(4):1285-1287).

**Reference Values:**
A reference range for specimens other than serum has not been established.

---

**Fungitell, Serum**

**Interpretation:** Glucan values of less than 60 pg/mL are interpreted as negative. Glucan values of 60 to 79 pg/mL are interpreted as indeterminate, and suggest a possible fungal infection. Additional sampling and testing of sera is required to interpret the results. Glucan values of greater than or equal to 80 pg/mL are interpreted as positive. Due to the potential for environmental contamination when transferred to pour-off tubes, which can lead to false positive results, interpret positive results from samples provided in pour-off tubes with caution. Results should be used in conjunction with clinical findings, and should not form the sole basis for a diagnosis or treatment decision. Fungitell is FDA approved or cleared for in vitro diagnostic use. The Fungitell assay does not detect certain fungal species such as the genus Cryptococcus (Tanaka et al. 1991) which produces very low levels of (1-3)-Beta-D-Glucan. The assay also does not detect the Zygomycetes such as Absidia, Mucor and Rhizopus (Mitsuya et al. 1994) which are not known to produce (1-3)-Beta-D-Glucan. In addition, the yeast phase of Blastomyces dermatitidis produces little (1-3)-Beta-D-Glucan and may not be detected by the assay (Girouard et al. 2007).

**Reference Values:**
Less than 60 pg/mL

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**Furosemide (Lasix)**

**Reference Values:**
Expected serum furosemide concentration in patients on usual daily dosages: Up to 5.0 ug/mL

Toxic: greater than 50.0 ug/mL

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**Fusarium moniliforme, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FFOVE 57531**

**Fusarium oxysporum/vasinfectum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**GABA 80826**

**Gabapentin, Serum**

**Clinical Information:** Gabapentin is an antiepileptic drug that is effective in treating seizures, neuropathies, and a variety of neurological and psychological maladies. Although designed as a gamma amino butyric acid (GABA) analogue, gabapentin does not bind to GABA receptors, nor does it affect the neuronal uptake or degradation of GABA. In fact, the precise mechanism by which it exerts its analgesic and anticonvulsant effects is unknown. After oral administration and absorption, gabapentin circulates essentially unbound to serum proteins. In addition, gabapentin does not undergo hepatic metabolism unlike most other antiepileptic drugs and is eliminated almost entirely by renal excretion with a clearance that approximates the glomerular filtration rate. The elimination half-life is 5 to 7 hours in patients with normal renal function. Since gabapentin does not bind to serum proteins, it does not exhibit pharmacokinetic variability and interactions with other highly protein-bound medications (ie, phenytoin). In addition, the lack of hepatic metabolism eliminates the interactions with other hepatically cleared medications which can induce/inhibit hepatic drug metabolizing enzyme systems (cytochrome P450s). Therefore, gabapentin serum concentrations are not changed following the addition or discontinuation of other common anticonvulsants (ie, phenobarbital, phenytoin, carbamazepine, or valproic acid), nor are their serum concentration altered upon the addition or discontinuation of gabapentin. In general, adverse effects with gabapentin are infrequent and usually resolve with continued treatment. The most common side effects include somnolence, dizziness, ataxia, and fatigue. Experience to date indicated that gabapentin is safe and relatively nontoxic.
Useful For: Monitoring serum gabapentin concentrations Assessing compliance Adjusting dosage in patients

Interpretation: Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Most individuals display optimal response to gabapentin with serum levels of 2 to 20 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Some patients require high doses to achieve response, resulting in concentrations as high as 80 mcg/mL. Dosage reduction should be based on signs of toxicity, not the serum concentration.

Reference Values:
2.0-20.0 mcg/mL

Toxic Range: > or =25.0 mcg/mL


FGABA
Gabapentin, Urine
Reference Values:
Reference Range: Not Established

Units: ug/mL

GDU
Gadolinium, 24 Hour, Urine
Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media for magnetic resonance imaging and computer tomography scanning. Gadolinium is eliminated primarily by the renal filtration. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes. Patients with reduced renal function exhibit an increased gadolinium excretion half-life. Gadolinium has been associated with nephrogenic systemic fibrosis (NSF) in patients with impaired renal function. In this syndrome, prolonged retention of gadolinium is thought to allow the gadolinium cation to dissociate from its synthetic organic chelator and deposit predominantly in the skin, although other organs may be affected as well. These patients are often severely debilitated by progressive skin thickening and tightening. Fibrosis of skeletal muscle, lungs, liver, testes, and myocardium have also been observed, often with fatal results. Because the ionic radius of gadolinium (3+) is similar to that of calcium (2+), it may also deposit in bone. Three hemodialysis treatments are required to substantially remove gadolinium from patients with impaired renal function; peritoneal dialysis is not effective.

Useful For: An aid in documenting past exposure to gadolinium-containing chelates

Interpretation: Elevated gadolinium (>0.5 mcg/specimen) observed in a 24-hour urine specimen collected >96 hours after administration of gadolinium-containing contrast media may indicate impaired ability to eliminate gadolinium or continued exposure, suggesting either reduced renal function or exposure to anthropogenic sources. Patients with reduced renal function who have been exposed to gadolinium may have an increased risk to develop nephrogenic systemic fibrosis (NSF). Elevated gadolinium in a specimen collected <96 hours after contrast media infusion does not indicate risk of NSF. The normal value is <0.5 mcg/specimen; 95% of unexposed patients will have values <0.1 mcg/specimen. The lower limit of detection is 0.1 mcg/specimen.
Reference Values:
0.0-0.4 mcg/specimen
Reference values apply to all ages.


Gadolinium, Dermal, Tissue

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media for magnetic resonance imaging (MRI) and computer tomography (CT) scanning. Gadolinium is eliminated primarily by the renal filtration. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes. Patients with reduced renal function exhibit increased gadolinium excretion half-life. Patient with reduced renal function exposed to gadolinium chelates used as MRI or CT contrast media may be affected by nephrogenic systemic fibrosis (NSF). In this syndrome, prolonged retention of gadolinium is thought to allow the gadolinium cation to dissociate from its synthetic organic chelator and deposit predominantly in the skin, although other organs may be affected as well. These patients are often severely debilitated by progressive skin thickening and tightening. Fibrosis of skeletal muscle, lungs, liver, testes, and myocardium have also been observed, often with fatal results. Three hemodialysis treatments are required to substantially remove gadolinium from patients with impaired renal function; peritoneal dialysis is not effective.

Useful For: Evaluation of dermal tissue for gadolinium

Interpretation: Elevated gadolinium (>0.5 mcg/g) observed in affected dermal tissue specimens collected more than 48 hours after administration of gadolinium-containing contrast media indicates gadolinium deposition. These patients may have increased risk of nephrogenic systemic fibrosis (NSF). In individuals with NSF, affected tissues are likely to contain gadolinium at concentrations in the range of 4 to 186 mcg/g. Unaffected tissues from gadolinium-exposed subjects exhibit gadolinium concentration of 0.6 to 28 mcg/g. A reportable gadolinium concentration in tissue suggests recent administration of gadolinium-containing contrast media. Patients with increased gadolinium in affected dermal tissue have an increased risk to develop NSF.

Reference Values:
<0.5 mcg/g


Gadolinium, Random, Urine

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media for magnetic resonance imaging and computer tomography scanning. Gadolinium is eliminated primarily by renal filtration. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes. Patients with reduced renal function exhibit an increased gadolinium excretion half-life. Gadolinium has been associated with the nephrogenic systemic fibrosis in patients with impaired renal function. In this syndrome, prolonged retention of gadolinium is thought to allow the gadolinium cation to dissociate from its synthetic organic chelator and deposit predominantly in the skin, although other organs may be affected as well. These patients are often severely debilitated by progressive skin thickening and tightening. Fibrosis of skeletal muscle, lungs, liver, testes, and myocardium have all been observed, often with fatal results. Because the ionic radius of gadolinium (3+) is similar to that of calcium (2+), it may also deposit in bone.

Useful For: An aid in documenting past exposure to gadolinium-containing chelates

Interpretation: Elevated gadolinium (>0.5 mcg/L) observed in a random urine specimen collected >96 hours after administration of gadolinium-containing contrast media may indicate impaired ability to eliminate gadolinium or continued exposure, suggesting either reduced renal function or exposure to anthropogenic sources. Patients with reduced renal function who have been exposed to gadolinium may have an increased risk to develop nephrogenic systemic fibrosis. The normal value is <0.5 mcg/L; 95% of unexposed patients will have values <0.1 mcg/L. The lower limit of detection is 0.1 mcg/L.

Reference Values:
0.0-0.4 mcg/L
Reference values apply to all ages.

Clinical References:

Gadolinium, Serum

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media for magnetic resonance imaging and computer tomography scanning. Gadolinium is eliminated primarily by the renal filtration. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes. Patients with
reduced renal function exhibit an increased gadolinium excretion half-life. Gadolinium has been associated with the nephrogenic systemic fibrosis in patients with impaired renal function. In this syndrome, prolonged retention of gadolinium is thought to allow the gadolinium cation to dissociate from its synthetic organic chelator and deposit predominantly in the skin, although other organs may be affected as well. These patients are often severely debilitated by progressive skin thickening and tightening. Fibrosis of skeletal muscle, lungs, liver, testes, and myocardium have also been observed, often with fatal results. Because the ionic radius of gadolinium (3+) is similar to that of calcium (2+), it may also deposit in bone. Three hemodialysis treatments are required to substantially remove gadolinium from patients with impaired renal function; peritoneal dialysis is not effective.

**Useful For:** An aid in documenting past exposure to gadolinium-containing chelates

**Interpretation:** Elevated gadolinium (>3 ng/mL) observed in serum specimens drawn >96 hours after administration of gadolinium-containing contrast media is not typical of most patients with normal renal function, indicating impaired elimination of gadolinium or exposure to anthropogenic sources. Patients with reduced renal function who have been exposed to gadolinium may have an increased risk to develop nephrogenic systemic fibrosis. A normal value is <0.5 ng/mL; the lower limit of the assay's reportable range is 0.1 ng/mL.

**Reference Values:**
<0.5 ng/mL

**Clinical References:**

**Gadolinium/Creatinine Ratio, Random, Urine**

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media for magnetic resonance imaging and computer tomography scanning. Gadolinium is eliminated primarily by renal filtration. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes. Patients with reduced renal function exhibit an increased gadolinium excretion half-life. Gadolinium has been associated with the nephrogenic systemic fibrosis in patients with impaired renal function. In this syndrome, prolonged retention of gadolinium is thought to allow the gadolinium cation to dissociate from its synthetic organic chelator and deposit predominantly in the skin, although other organs may be affected as well. These patients are often severely debilitated by progressive skin thickening and tightening. Fibrosis of skeletal muscle, lungs, liver, testes, and myocardium have all been observed, often with fatal results. Because the ionic radius of gadolinium (3+) is similar to that of calcium (2+), it may also deposit in bone. Three hemodialysis treatments are required to substantially remove gadolinium from patients with impaired renal function; peritoneal dialysis is not effective.

**Useful For:** An aid in documenting past exposure to gadolinium-containing chelates and to monitor the effectiveness of dialysis

**Interpretation:** Elevated gadolinium (>0.5 mcg/g creatinine) observed in a random urine specimen collected >96 hours after administration of gadolinium-containing contrast media may indicate impaired ability to eliminate gadolinium or continued exposure, suggesting either reduced renal function or exposure to anthropogenic sources. Patients with reduced renal function who have been exposed to
Gadolinium may have an increased risk to develop nephrogenic systemic fibrosis. The normal value is <0.5 mcg/g creatinine; 95% of unexposed patients will have values <0.1 mcg/g creatinine. The lower limit of detection is 0.1 mcg/g creatinine.

**Reference Values:**
0.0-0.4 mcg/g Creatinine

Reference values apply to all ages.

**Clinical References:**

**Galactitol, Quantitative, Urine**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, cognitive and intellectual disabilities, and death. Galactosemia is treated with a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, abnormalities of motor function, and females are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000. Galactose levels may be continuously elevated in individuals affected with galactosemia even with a galactose-restricted diet regimen due to an endogenous production of galactose. The reduction of galactose to galactitol is an alternate pathway of galactose disposition when galactose metabolism is impaired. The excretion of abnormal quantities of galactitol in the urine of patients is characteristic of this disorder, and patients may have abnormal levels of galactitol even with dietary compliance. Daily consumption of galactose may cause urine levels to rise thus providing information on effectiveness of or compliance with treatment, but unlike erythrocyte galactose-1-phosphate (GAL1P) and plasma galactose, urine galactitol levels usually do not provide insight into acute and transient effects of galactose intake.

**Useful For:** Monitoring effectiveness of treatment in patients with galactosemia
Establishing a baseline level prior to initiating treatment for galactosemia

**Interpretation:** The concentration of galactitol is provided along with reference ranges for patients with galactosemia and normal controls.

**Reference Values:**
- 0-11 months: <109 mmol/mol creatinine
- 1-3 years: <52 mmol/mol creatinine
- 4-<17 years: <16 mmol/mol creatinine
- > or =18 years: <13 mmol/mol creatinine

**Clinical References:**
1. Online Mendelian Inheritance in Man. 230400, 230200, and 230350,
C6GT

Galactocerebrosidase, Fibroblasts

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase. A deficiency of this enzyme leads to an accumulation of galactosylerosidase causing severe demyelination throughout the brain. Krabbe disease is primarily caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A (SAP-A) have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. A small subset of individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has recently been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Reduced or absent galactocerebrosidase in fibroblasts or leukocytes (CBGC / Galactocerebrosidase, Leukocytes) can indicate a diagnosis of Krabbe disease, however a number of polymorphisms in the GALC gene have been identified that result in reduced galactocerebrosidase activity in vitro, but by themselves do not cause disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) allows for detection of the disease-causing mutations in affected patients and carrier detection in family members.

Useful For: Diagnosis of Krabbe disease

Interpretation: Values below the reference range are consistent with a diagnosis of Krabbe disease.

Reference Values:
> or =1.20 nmol/h/mg protein

Clinical References:

CBGC

Galactocerebrosidase, Leukocytes

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase. A deficiency of this enzyme leads to an accumulation of galactosylceramide causing severe demyelination throughout the brain. Krabbe disease is primarily caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A (SAP-A) have been found. Saposin-A is a sphingolipid activator protein that assists
galactocerebrosidase in its action on galactosylceramide. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. A small subset of individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has recently been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Reduced or absent galactocerebrosidase in leukocytes or fibroblasts (CBGT / Galactocerebrosidase, Fibroblasts) can indicate a diagnosis of Krabbe disease, however a number of polymorphisms in the GALC gene have been identified that result in reduced galactocerebrosidase activity in vitro, but by themselves do not cause disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) allows for detection of the disease-causing mutations in affected patients and carrier detection in family members.

**Useful For:** Diagnosis of Krabbe disease

**Interpretation:** Values below the reference range are consistent with a diagnosis of Krabbe disease. The upper limit of normal may change with the specific activity of the substrate. Elevated values have no known clinical significance.

**Reference Values:**
> or =1.20 nmol/h/mg protein

**Clinical References:**

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**Galactokinase, Blood**

**Clinical Information:** Galactokinase (GALK) deficiency is the second most common form of galactosemia, affecting approximately 1/250,000 live births, with a higher frequency in the Romani population. Individuals with GALK deficiency have a milder clinical presentation than that seen in patients with classic galactosemia, galactose-1-phosphate uridyltransferase (GALT) deficiency. The major clinical manifestation is bilateral juvenile cataracts. GALK deficiency is treated with a lactose-restricted diet. Early treatment may prevent or reverse the formation of cataracts. In GALK deficiency, erythrocyte galactose-1-phosphate levels are generally normal and plasma galactose levels are generally elevated. The diagnosis is established by demonstrating deficient GALK enzyme activity in erythrocytes. Testing for GALK deficiency should be performed when there is a suspicion of galactosemia, either based upon the patient's clinical presentation or laboratory studies and GALT deficiency has been excluded. Specimens sent for GALT analysis may be used for GALK testing if the original specimen was received in the laboratory within 48 hours of draw. GALK deficiency is caused by mutations in the GALK1 gene. Gene analysis is available from some commercial laboratories. Contact Mayo Medical Laboratories for recommendations or contact information for laboratories that offer this testing. See Galactosemia Testing Algorithm in Special Instructions.

**Useful For:** Diagnosis of galactokinase deficiency, the second most common cause of galactosemia

**Interpretation:** Low values suggest galactokinase deficiency. Only results below the normal range are clinically significant. Elevated values have no clinical significance. See Galactosemia Testing Algorithm
Reference Values:
<2 years: 20.1-79.8 mU/g of hemoglobin
≥2 years: 12.1-39.7 mU/g of hemoglobin

Clinical References:

GALP
83638

Galactose, Quantitative, Plasma

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia. For more information regarding diagnostic strategy, refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5). See Galactosemia Testing Algorithm in Special Instructions for additional information. Deficiency Galactose (Plasma/Urine) Gal-1-P (Blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated

Useful For: Screening for galactosemia

Interpretation: Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn, and, in rare cases, galactose intolerance. If results are outside the normal range and galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. See GALT / Galactose-1-Phosphate Uridyltransferase (GALT), Blood for GALT testing, GALK / Galactokinase, Blood for GALK testing, and GALE / UDP-Galactose-4â€™Epimerase (GALE), Blood for GALE testing.

Reference Values:
1-7 days: <5.4 mg/dL
8-14 days: <3.6 mg/dL
>14 days: <2.0 mg/dL

Galactose, Quantitative, Urine

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylytransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia; however, these are only general patterns and further confirmatory testing would be required to make a diagnosis. Deficiency Galactose (Plasma/Urine) Gal-1-P (Blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated For more information regarding diagnostic strategy, refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5). See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Useful For:** Screening test for galactosemia

**Interpretation:** Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn, and, in rare cases, galactose intolerance. If galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. See GALT / Galactose-1-Phosphate Uridylytransferase (GALT), Blood for GALT testing and GALK / Galactokinase, Blood for GALK testing, and GALE / UDP-Galactose 4' Epimerase (GALE), Blood for GALE testing. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis.

**Reference Values:**

<30 mg/dL


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Galactose-1-Phosphate (Gal-1-P), Erythrocytes

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylytransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia; however, these are only general patterns and further confirmatory testing would be required to make a diagnosis. Deficiency Galactose (Plasma/Urine) Gal-1-P (Blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated For more information regarding diagnostic strategy, refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5). See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Useful For:** Screening test for galactosemia

**Interpretation:** Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn, and, in rare cases, galactose intolerance. If galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. See GALT / Galactose-1-Phosphate Uridylytransferase (GALT), Blood for GALT testing and GALK / Galactokinase, Blood for GALK testing, and GALE / UDP-Galactose 4' Epimerase (GALE), Blood for GALE testing. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis.

**Reference Values:**

<30 mg/dL

uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency. The quantitative measurement of Gal-1-P (GAL1P / Galactose-1-Phosphate (Gal-1-P), Erythrocytes) is useful for monitoring compliance with dietary therapy for either deficiency. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. The concentration of Gal-1-P in erythrocytes is the most sensitive index of dietary control. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia due to GALT deficiency is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared with intermediate epimerase deficiency galactosemia, which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and renal dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of renal and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, females with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6,700 in African American infants to 1 in 70,000 in infants of European ancestry. For more information regarding diagnostic strategy, refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communiqué 2005 May;30(5). See Galactosemia Testing Algorithm in Special Instructions.

Useful For: Monitoring dietary therapy of patients with galactosemia due to deficiency of galactose-1-phosphate uridylyltransferase or uridine diphosphate galactose-4-epimerase

Interpretation: The concentration of galactose-1-phosphate (Gal-1-P) is provided along with reference ranges for patients with galactosemia and normal controls. The recommended Gal-1-P goal for patients with galactosemia is <125 mcg/g of hemoglobin. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Reference Values:
Non-galactosemic: 5-49 mcg/g of hemoglobin (<1 mg/dL)
Galactosemic on galactose restricted diet: 80-125 mcg/g of hemoglobin (1-4 mg/dL)
Galactosemic on unrestricted diet: >125 mcg/g of hemoglobin (>4 mg/dL)

Galactose-1-Phosphate Uridyltransferase (GALT), Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can occur. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal-1-P is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia (compound heterozygosity for the Duarte mutation, N314D, and a classic mutation) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte-variant galactosemia have a milder phenotype, but are also often treated with a low galactose diet during infancy. The Los Angeles variant, which consists of N314D and a second mutation, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutations. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Diagnosis of galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia Confirmation of abnormal state newborn screening results

Interpretation: An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information. For galactokinase deficiency, see GALK / Galactokinase, Blood. For galactokinase deficiency, see GALK / Galactokinase, Blood. For epimerase deficiency, see GALE / UDP-Galactose 4' Epimerase, Blood.

Reference Values:
> or =24.5 nmol/h/mg of hemoglobin


Galactose-1-Phosphate Uridyltransferase Biochemical Phenotyping, Erythrocytes

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase.
uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Duarte-variant galactosemia (compound heterozygosity for the Duarte mutation, N314D, and a classic mutation) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte-variant galactosemia have a milder phenotype, but are also often treated with a low galactose diet during infancy. The LA variant, which consists of N314D and a second mutation, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. In general, molecular genetic analysis with a panel of common mutations is typically performed to determine the specific genotype. If the enzymatic and molecular results are incongruent, biochemical phenotyping and/or molecular sequence analysis may be beneficial to help clarify results to determine a treatment strategy and recurrence risks. For more information regarding diagnostic strategy, refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5). See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Determining the biochemical phenotype for galactosemia when enzymatic and molecular results are incongruent. A quantitative galactose-1-phosphate uridyltransferase level (GALT / Galactose-1-Phosphate Uridyltransferase [GALT], Blood) is required for accurate interpretation.

Interpretation: An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Reference Values:
Descriptive report

Clinical References:

Galactose-alpha-1,3-galactose (Alpha-Gal) IgE

Interpretation:

Reference Values:
<0.35 kU/L

Previous reports (JACI 2009; 123:426-433) have demonstrated that patients with IgE antibodies to galactose-a-1,3-galactose are at risk for delayed anaphylaxis, angioedema, or urticaria following consumption of beef, pork, or lamb.

Galactosemia Gene Analysis (14-Mutation Panel)

Clinical Information: Classical galactosemia is an autosomal recessive disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated,
complications include liver failure, sepsis, mental retardation, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte mutation, N314D and -119_-116delGTCA in cis [on the same chromosome], and a classic mutation in trans [on the opposite chromosome]) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are also often treated with a low-galactose diet during infancy. The Los Angeles (LA) variant, which consists of N314D without the presence of -119_-116delGTCA, is associated with normal levels of GALT enzyme activity. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutations. The GALT gene maps to 9p13. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic mutation. This mutation accounts for 60% to 70% of classical galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classical galactosemia. The 5 kb deletion is common in individuals of Ashkenazi Jewish descent. The Duarte mutation (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the mutations detected by this method (ie, D98N, S135L, T138M, M142K, F171S, Y209C, and Q344K) are all uncommon, but known to be recurrent in the general population. These mutations, in addition to the LA variant, are included in GAL14 / Galactosemia Gene Analysis (14-Mutation Panel) and in GCT / Galactosemia Reflex, Blood. See Galactosemia Testing Algorithm in Special Instructions for additional information. Refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5) for more information regarding diagnostic strategy.

**Useful For:** Second-tier test for confirming a diagnosis of galactosemia (indicated by enzymatic testing or newborn screening) Carrier testing family members of an affected individual of known genotype (has mutations included in the panel) Resolution of Duarte variant and Los Angeles (LA) variant genotypes

**Interpretation:** An interpretative report will be provided. Results should be interpreted in the context of biochemical results.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Galactosemia Reflex, Blood**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can occur. Galactosemia is treated by a
The galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births.

Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal-1-P is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia (compound heterozygosity for the Duarte mutation, N314D, and a classic mutation) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte-variant galactosemia have a milder phenotype, but are also often treated with a low galactose diet during infancy. The Los Angeles variant, which consists of N314D and a second mutation, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutations. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Diagnosis, carrier detection, and determination of genotype of galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia Differentiating Duarte variant galactosemia from classic galactosemia Confirming results of newborn screening programs

Interpretation: The laboratory provides an interpretation of the results, including galactose-1-phosphate uridyltransferase enzyme activity and genotype, if necessary. This interpretation provides an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional testing. Any specimen where enzyme activity is <24.5 nmol/h/mg of hemoglobin will be analyzed for the presence of 14 mutations associated with classic galactosemia, as well as the 2 variants (Duarte and Los Angeles). See Galactosemia Reflex Algorithm in Special Instructions for testing algorithm and additional information. The GALT gene maps to 9p13. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic mutation. This mutation accounts for 60% to 70% of classical galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classical galactosemia. The 5 kb deletion is common in individuals of Ashkenazi Jewish descent. The Duarte mutation (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the mutations detected by this method (ie, D98N, S135L, T138M, M142K, F171S, Y209C, and Q344K) are all uncommon, but known to be recurrent in the general population. A high proportion (20%) of patients with classic galactosemia have a private mutation. Since our assay does not investigate for the presence of private mutations, when GG, DG, or NG genotype is predicted by enzymatic studies and the current panel does not identify a mutation, molecular sequencing may be indicated.

Reference Values:
> or =24.5 nmol/h/mg of hemoglobin

Galectin-3, Serum

Clinical Information: Heart failure is a complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are readmitted within the forthcoming year, incurring costly treatments and therapies. The development and progression of heart failure is a clinically-silent process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically, heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury and/or stress. Galectin-3 is a biomarker which appears to be actively involved in both the inflammatory and fibrotic pathways that are thought to be involved. Galectin-3 is a carbohydrate-binding lectin whose expression is associated with inflammatory cells including macrophages, neutrophils, and mast cells. Galectin-3 has been linked to cardiovascular physiological processes including myofibroblast proliferation, tissue repair, and cardiac remodeling in the setting of heart failure. Concentrations of galectin-3 have been used to predict adverse remodeling after a variety of cardiac insults.

Useful For: An aid in prognosis for patients diagnosed with heart failure Risk-stratification of heart failure patients An early indication of treatment failure and as a therapeutic target

Interpretation: Clinically, galectin-3 concentrations may be categorized into 3 risk categories, substantiated by results from several large chronic heart failure studies: (2-4) < or =17.8 ng/mL (low risk) 17.9-25.9 ng/mL (intermediate risk) >25.9 ng/mL (higher risk) Results should be interpreted in the context of the individual patient presentation. Elevated galectin-3 results indicate an increased risk for adverse outcomes and signal the presence of galectin-3-mediated fibrosis and adverse remodeling. Once galectin-3 concentrations are elevated they are relatively stable over time in the absence of intervention. Knowledge of a heart failure patient’s galectin-3 results may assist in risk stratification and lead to more aggressive management. There are no specific galectin-3 inhibitors available at this time and heart failure patients with elevated galectin-3 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers (ARBs) and aldosterone antagonists are thought to be particularly effective. A large multicenter, prospective, observational study was conducted to derive the reference intervals for galectin-3 which included 1,092 subjects between the ages of 55 and 80 years without any known cardiac disease (520 males, 572 females). The 97.5th percentile of galectin-3 in that cohort was 22.1 ng/mL. Individuals with concentrations >22.1 ng/mL had a significant association with mortality and New York Heart Association (NYHA) classification. However, this was an older population and definitive evidence of cardiac disease was not documented.

Reference Values:
<18 years: not established
> or =18 years: < or =22.1 ng/mL

Clinical References:
GALT Gene, Full Gene Analysis

**Clinical Information:** Classic galactosemia is an autosomal recessive disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, mental retardation, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D, and a classic mutation) is generally associated with higher levels of GALT activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype, but are often treated with a low galactose diet during infancy. The LA variant, consisting of N314D and a second change, L218L, is associated with higher levels of GALT activity than the Duarte variant alone. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT activity. If enzyme activity levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutation(s). The GALT gene maps to 9p13. More than 180 mutations have been identified in the GALT gene. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R mutation. This mutation accounts for 60% to 70% of classic galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classic galactosemia. The Duarte variant (N314D) is found in 5% of the general United States population. The above mutations, plus the LA variant, are included in GCT / Galactosemia Reflex, Blood, which is the preferred test for the diagnosis of galactosemia or for follow-up to positive newborn screening results. These mutations are also included in GAL14 / Galactosemia Gene Analysis (14-Mutation Panel). Full sequencing of the GALT gene can be useful for the identification of mutations when 1 or no mutations are found with these tests in an individual with demonstrated GALT activity deficiency. Full sequencing of the GALT gene identifies over 95% of the sequence variants in the coding region and splice junctions. See Galactosemia Testing Algorithm in Special Instructions for additional information. Refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5) for more information regarding diagnostic strategy.

**Useful For:** Identifying mutations in individuals who test negative for the common mutations and who have a biochemical diagnosis of galactosemia or galactose-1-phosphate uridyltransferase activity levels indicative of carrier status

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Gamma-Glutamyltransferase (GGT), Serum**

**Clinical Information:** Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Small amounts are present in other tissues. Even though renal tissue has the highest level of GGT, the enzyme present in the serum appears to originate primarily from the hepatobiliary system, and GGT activity is elevated in any and all forms of liver disease. It is highest in cases of intra- or post-hepatic biliary obstruction, reaching levels some 5 to 30 times normal. It is more sensitive than alkaline phosphatase (ALP), leucine aminopeptidase, aspartate transaminase, and alanine aminotransferase in detecting obstructive jaundice, cholangitis and cholecystitis; its rise occurs earlier than with these other enzymes and persists longer. Only modest elevations (2-5 times normal) occur in infectious hepatitis, and in this condition GGT determinations are less useful diagnostically than are measurements of the transaminases. High elevations of GGT are also observed in patients with either primary or secondary (metastatic) neoplasms. Elevated levels of GGT are noted not only in the sera of patients with alcoholic cirrhosis but also in the majority of sera from persons who are heavy drinkers. Studies have emphasized the value of serum GGT levels in detecting alcohol-induced liver disease. Elevated serum values are also seen in patients receiving drugs such as phenytoin and phenobarbital, and this is thought to reflect induction of new enzyme activity. Normal values are observed in various muscle diseases and in renal failure. Normal values are also seen in cases of skeletal disease, children older than 1 year and in healthy pregnant women-conditions in which ALP is elevated.

**Useful For:** Diagnosing and monitoring hepatobiliary disease, it is currently the most sensitive enzymatic indicator of liver disease. Ascertaining whether observed elevations of alkaline phosphatase are due to skeletal disease (normal gamma-glutamyltransferase: GGT) or reflect the presence of hepatobiliary disease (elevated GGT) A screening test for occult alcoholism

**Interpretation:** An elevation of gamma-glutamyltransferase (GGT) activity is seen in any and all forms of liver disease, although the highest elevations are seen in intra- or post-hepatic biliary obstruction. Elevated values can also indicate alcoholic cirrhosis or individuals who are heavy drinkers. The finding of increased GGT and alkaline phosphatase (ALP) activity is consistent with hepatobiliary disease. The finding of normal GGT activity and increased ALP activity is consistent with skeletal disease.

**Reference Values:**

**Males**
- 1-6 years: 7-19 U/L
- 7-9 years: 9-22 U/L
- 10-13 years: 9-24 U/L
- 14-15 years: 9-26 U/L
- 16-17 years: 9-27 U/L
- 18-35 years: 9-31 U/L
- 36-40 years: 8-35 U/L
- 41-45 years: 9-37 U/L
- 46-50 years: 10-39 U/L
- 51-54 years: 10-42 U/L
- 55 years: 11-45 U/L
- > or =56 years: 12-48 U/L

Reference values have not been established for patients <12 months of age.

**Females**
- >1 year: 6-29 U/L

Reference values have not been established for patients <12 months of age.

**Clinical References:**
2. Package insert: Boehringer Mannheim GGT reagent, Indianapolis, IN, September 1998
**Gamma-Hydroxybutyric Acid (GHB), Serum/Plasma**

**Reference Values:**
Reference Range: Negative

Screening threshold: 5.0 ug/mL

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**Gamma-Hydroxybutyric Acid (GHB), Urine**

**Reference Values:**
Reference Range: Negative

Screening threshold: 5.0 ug/mL

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**Ganciclovir, Serum**

**Clinical Information:** Ganciclovir, an analog of acyclovir, demonstrates inhibitory action against some viruses including herpes virus, cytomegalovirus, and HIV. Therapeutic ranges have not been well-established for ganciclovir; current ranges are based on typical values seen during ganciclovir therapy and do not correlate well to toxicity or outcome. Monitoring of ganciclovir serum concentrations may be most useful in guiding therapy in patients with renal dysfunction. Myelosuppression is the major dose-limiting side effect of ganciclovir. Valcyte (valganciclovir) is an oral prodrug of ganciclovir ester. It is immediately converted to ganciclovir once it enters the bloodstream. The oral dose is designed to deliver ganciclovir equivalent to intravenous ganciclovir at 5 mg/kg.

**Useful For:** Monitoring patients on ganciclovir

**Interpretation:** Serum concentrations of ganciclovir do not correlate well to toxicity or efficacy. Peak and trough levels provided are representative of typical serum concentrations seen during therapy, but individual values must be interpreted in conjunction with the clinical status of the individual patient and the specific characteristics of the infecting microorganism.

**Reference Values:**
Trough: 1.0-3.0 mcg/mL  
Peak: 3.0-12.5 mcg/mL

**Clinical References:**  

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**Ganglioside (Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b) Antibodies**

**Interpretation:** Ganglioside antibodies are associated with diverse peripheral neuropathies. Elevated antibody levels to ganglioside-monosialic acid (GM1) and the neutral glycolipid, asialo-GM1 are associated with motor or sensorimotor neuropathies, particularly multifocal motor neuropathy. Anti-GM1 may occur as IgM (polyclonal or monoclonal) or IgG antibodies. These antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals. GD1a antibodies are associated with different variants of Guillain-Barre syndrome (GBS) particularly acute motor axonal neuropathy while GD1b antibodies are predominantly found in sensory ataxic neuropathy syndrome. Anti-GQ1b antibodies are seen in more than 80 percent of patients with Miller-Fisher syndrome and may be elevated in GBS patients with ophthalmoplegia. The role of isolated anti-GM2 antibodies is unknown. These tests by themselves are not diagnostic and should be used in conjunction with other clinical parameters to confirm disease.
**Reference Values:**

- **29 IV or less:** Negative
- **30 â€“ 50 IV:** Equivocal
- **51 â€“ 100 IV:** Positive
- **101 IV or greater:** Strong Positive

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**Ganglioside Antibody Panel, Serum**

**Clinical Information:** Peripheral neuropathies are a group of disorders that result from lesions on peripheral nerves. Patients with a peripheral neuropathy can have symptoms of weakness, sensory loss, and/or autonomic dysfunction. The causes of acquired peripheral neuropathies are varied, and include vitamin deficiencies, metabolic abnormalities, infections, malignancies (paraneoplastic disorders), and autoimmune diseases. A subset of the autoimmune-mediated peripheral neuropathies is associated with the presence of circulating autoantibodies that bind to specific gangliosides. Gangliosides are glycosphingolipids that contain sialic acid residues. Although present in the plasma membranes of many cell types, gangliosides are particularly abundant in neural tissue. Guillain-Barre syndrome is one class of autoimmune peripheral neuropathies, and comprises a spectrum of disorders including acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy. This class of autoimmune neuropathies is generally characterized by an acute onset. Although the diagnosis of these disorders is based significantly on clinical evaluation and electrophysiologic studies, assessment of ganglioside antibodies, particularly against GM1, asialo GM1, and GD1b, can provide useful information. It is thought that the Guillain-Barre syndrome disorders are triggered by an infection, which results in production of infection-associated lipooligosaccharide-specific antibodies. These antibodies subsequently bind to endogenous gangliosides, due to molecular mimicry, which leads to immune-mediated damage to the peripheral nerves, ultimately resulting in the clinical symptoms associated with the disorders.\(^{(1)}\)

**Useful For:** Supporting diagnosis of neurological diseases—primarily motor neuron disease and motor neuropathies

**Interpretation:** High titers (>1:2,000) have been found only in patients with multifocal motor neuropathy and not with motor neuron disease. About 30% to 50% of patients with these clinical syndromes or the pure motor variant of chronic inflammatory demyelinating polyneuropathy have increased antibody titers. Increased antibody titers, therefore, appear to be a specific but not sensitive marker of those related disorders. Borderline elevation of titers against ganglioside epitopes may be seen in patients with motor neuron disease or motor neuropathy. For IgG and IgM antibodies directed against monosialo GM1 and disialo GD1b, 99% of 182 age- and sex-stratified normal individuals had titers <1:1,000; 99% of 121 patients with well-defined motor neuron disease had titers <1:2,000; and all patients with titers >1:2,000 had motor neuropathy.

**Reference Values:**

- IgG monosialo GM1 1:500
- IgM monosialo GM1 1:1,000
- IgG asialo GM1 1:4,000
- IgM asialo GM1 1:4,000
- IgG disialo GD1b 1:1,000
- IgM disialo GD1b 1:1,000 Borderline Ranges
- IgG monosialo GM1 =1:1,000
- IgM monosialo GM1 =1:2,000
- IgG asialo GM1 =1:8,000
- IgM asialo GM1 No borderline range (normal: < or =4,000)
IgG disialo GD1b  No borderline range (normal: < or =1,000)
IgM disialo GD1b  No borderline range (normal: < or =1,000)

Abnormal Results

IgG monosialo GM1  >1:1,000
IgM monosialo GM1  >1:2,000
IgG asialo GM1  >1:8,000
IgM asialo GM1  >1:4,000
IgG disialo GD1b  >1:1,000
IgM disialo GD1b  >1:1,000


FGQ1B  Ganglioside GQ1b Antibody (IgG), EIA

Reference Values:
Less than 1:100 titer

FGARG  Garlic IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

GARL  Garlic, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
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<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
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<td>&gt; or =100</td>
<td>Strongly positive</td>
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</tbody>
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Reference values apply to all ages.


**GAST 8512**

**Clinical Information:** Gastrin is a peptide hormone produced by mucosal G cells of the gastric antrum. It is synthesized as preprogastrin, cleaved to progastrin, which undergoes several posttranslational modifications, in particular sulfation, and is finally processed into the mature 34-amino acid, gastrin-34. Gastrin-34 may be cleaved further into the shorter 17-amino acid, gastrin-17. Either may be secreted as a C-terminal amidated or unamidated isoform. A number of additional, smaller gastrin fragments, as well as gastrin molecules with atypical posttranslational modifications (eg, absent sulfation), may also be secreted in small quantities. Gastrin half-life is short, 5 minutes for amidated gastrin-17, and 20 to 25 minutes for amidated gastrin-34. Elimination occurs through peptidase cleavage and renal excretion. Gastrin-17 I (nonsulfated form) and gastrin-17 II (sulfated) appear equipotent. Their biological effects are chiefly associated with the amidated isoforms and consist of promotion of gastric epithelial cell proliferation and differentiation to acid-secreting cells, direct promotion of acid secretion, and indirect stimulation of acid production through histamine release. In addition, gastrin stimulates gastric motility and release of pepsin and intrinsic factor. Most gastrin isoforms with atypical posttranslational modifications and most small gastrin fragments display reduced or absent bioactivity. This assay measures predominately gastrin-17. Larger precursors and smaller fragments have little or no cross-reactivity in the assay. Intraluminal stomach pH is the main factor regulating gastrin production and secretion. Rising gastric pH levels result in increasing serum gastrin levels, while falling pH levels are associated with mounting somatostatin production in gastric D cells. Somatostatin, in turn, downregulates gastrin synthesis and release. Other, weaker factors that stimulate gastrin secretion are gastric distention, protein-rich foods, and elevated secretin or serum calcium levels. Serum gastrin levels may also be elevated in gastric distention due to gastric outlet obstruction, and in a variety of conditions that lead to real or functional gastric hypo- or achlorhydria (gastrin is secreted in an attempted compensatory response to achlorhydria). These include atrophic gastritis with or without pernicious anemia; a disorder characterized by destruction of acid-secreting (parietal) cells of the stomach, gastric dumping syndrome, and surgically excluded gastric antrum. In atrophic gastritis, the chronic cell-proliferative stimulus of the secondary hypergastrinemia may contribute to the increased gastric cancer risk observed in this condition. Gastrin levels are

fasting periods (3-8 hours) may be 50% to 60% higher than the 8-hour fasting value. There is no evidence that fasting serum gastrin levels differ between adults and children. Although 8-hour fasts are difficult or impossible to enforce in small children, serum gastrin levels after shorter periods (<100 pg/mL) are virtually never observed. Several provocative tests can be used to distinguish these patients from individuals with gastrinomas. Patients with gastrinoma, who have normal or only mildly to modestly increased fasting serum gastrin levels, respond with exaggerated serum gastrin increases to intravenous infusions of secretin or calcium. Because of its greater safety, secretin infusion is preferred. The best validated protocol calls for a baseline fasting gastrin measurement, followed by an injection of 2 clinical units of secretin per kg body weight (0.4 microgram/kg) over 1 minute and further serum gastrin specimens at 5-, 10-, 15-, 20-, and 30-minutes postinjection. A peak-gastrin increase of >200 pg/mL above the baseline value has >85% sensitivity and near 100% specificity for gastrinoma. Secretin or calcium infusion tests are not carried out in the clinical laboratory, but are usually performed at gastroenterology or endocrine testing units under the supervision of a physician. They are progressively being replaced (or supplemented) by imaging procedures, particularly duodenal and pancreatic endoscopic ultrasound. All patients with confirmed gastrinoma should be evaluated for possible multiple endocrine neoplasia type 1 (MEN 1), which is the underlying cause in approximately 25% of cases. If clinical, biochemical, or genetic testing confirms MEN 1, other family members need to be screened.

Reference Values:

<100 pg/mL

There is no evidence that fasting serum gastrin levels differ between adults and children. Although 8-hour fasts are difficult or impossible to enforce in small children, serum gastrin levels after shorter fasting periods (3-8 hours) may be 50% to 60% higher than the 8-hour fasting value.

Useful For: Investigation of patients with achlorhydria or pernicious anemia. Investigation of patients suspected of having Zollinger-Ellison syndrome. Diagnosis of gastrinoma; basal and secretin-stimulated serum gastrin measurements are the best laboratory tests for gastrinoma.

Interpretation: Achlorhydria is the most common cause of elevated serum gastrin levels. The most common cause for achlorhydria is treatment of gastroduodenal ulcers, nonulcer dyspepsia, or gastroesophageal reflux with proton pump inhibitors (substituted benzimidazoles, eg, omeprazole). Other causes of hypo- and achlorhydria include chronic atrophic gastritis with or without pernicious anemia, gastric ulcer, gastric carcinoma, and previous surgical or traumatic vagotomy. If serum B12 levels are significantly low (<150 ng/L), even if the intrinsic factor blocking antibody tests are negative, a serum gastrin level above the reference range makes it likely the patient is nonetheless suffering from pernicious anemia. Hypergastrinemia with normal or increased gastric acid secretion is suspicious of a gastrinoma (Zollinger-Ellison syndrome). Gastrin levels <100 pg/mL are observed so uncommonly in untreated gastrinoma patients with intact upper gastrointestinal anatomy as to virtually exclude the diagnosis. The majority (>60%) of patients with gastrinoma have very significantly elevated serum gastrin levels (>400 pg/mL). Levels of >1,000 pg/mL in a gastrinoma or duodenal-ulcer patient without previous gastric surgery, on no drugs, who has a basal gastric acid output of >15 mmol/hour (>5 mmol/hour in patients with prior acid-reducing surgery) are considered diagnostic of gastrinoma. If there are any doubts about gastric acid output, an infusion of 0.1 N HCl into the stomach reduces the serum gastrin in patients with achlorhydria, but not in those with gastrinoma. Other conditions that may be associated with hypergastrinemia in the face of normal or increased gastric acid secretion include gastric and, rarely, duodenal ulcers, gastric outlet obstruction, bypassed gastric antrum, and gastric dumping. Occasionally, diabetes mellitus, autonomic neuropathy with gastroparesis, pheochromocytoma, rheumatoid arthritis, thyrotoxicosis, and paraneoplastic syndromes can also result in hypergastrinemia with normal acid secretion. None of these conditions tends to be associated with fasting serum gastrin levels >400 pg/mL, and levels >1,000 pg/mL are virtually never observed. Several provocative tests can be used to distinguish these patients from individuals with gastrinomas. Patients with gastrinoma, who have normal or only mildly to modestly increased fasting serum gastrin levels, respond with exaggerated serum gastrin increases to intravenous infusions of secretin or calcium. Because of its greater safety, secretin infusion is preferred. The best validated protocol calls for a baseline fasting gastrin measurement, followed by an injection of 2 clinical units of secretin per kg body weight (0.4 microgram/kg) over 1 minute and further serum gastrin specimens at 5-, 10-, 15-, 20-, and 30-minutes postinjection. A peak-gastrin increase of >200 pg/mL above the baseline value has >85% sensitivity and near 100% specificity for gastrinoma. Secretin or calcium infusion tests are not carried out in the clinical laboratory, but are usually performed at gastroenterology or endocrine testing units under the supervision of a physician. They are progressively being replaced (or supplemented) by imaging procedures, particularly duodenal and pancreatic endoscopic ultrasound. All patients with confirmed gastrinoma should be evaluated for possible multiple endocrine neoplasia type 1 (MEN 1), which is the underlying cause in approximately 25% of cases. If clinical, biochemical, or genetic testing confirms MEN 1, other family members need to be screened.

Gastrointestinal Pathogen Panel, PCR, Feces

**Clinical Information:** Acute diarrheal syndromes are usually self-limiting, but may be complicated by dehydration, vomiting, and/or fever. Diagnostic testing and treatment may be required in some instances. Many bacterial enteric infections in the United States originate within the food supply chain. According to the CDC, in 2012 there were 19,531 laboratory-confirmed cases of infection with pathogens potentially transmitted through food in the United States; the number of infections, by pathogen, were as follows: Salmonella species (7,800), Campylobacter species (6,793), Shigella species (2,138), Cryptosporidium species (1,234), Shiga toxin-producing Escherichia coli non-O157 (551), Shiga toxin-producing Escherichia coli O157 (531), Vibrio species (193), Yersinia species (155), and Cyclospora cayetanensis (15). Giardia may also be transmitted through ingestion of contaminated food and water. There were 15,178 cases of giardiasis reported to the CDC in 2012. Since the clinical presentation may be very similar for many of these bacterial, viral, and parasitic pathogens, laboratory testing is required for definitive identification of the causative agent. Rapid multiplex panel detection of the most common agents of bacterial, viral, and parasitic enteric infections directly from stool specimens is sensitive, specific, and provides same-day results, obviating the need for culture, antigen testing, microscopy, or individual nucleic acid amplification tests. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Rapid detection of gastrointestinal infections caused by:
- Campylobacter species (Campylobacter jejuni/Campylobacter coli/Campylobacter upsaliensis)
- Clostridium difficile toxin A/B
- Plesiomonas shigelloides
- Salmonella species
- Vibrio species (Vibrio paraahemolyticus, Vibrio vulnificus, Vibrio cholerae)
- Vibrio cholerae
- Yersinia enterocolitica
- Enteropathogenic Escherichia coli (EAEC)
- Enterotoxigenic Escherichia coli (ETEC)
- Shiga toxin
- Escherichia coli O157
- Shigella/Enteroinvasive Escherichia coli (EIEC)
- Cryptosporidium species
- Cyclospora cayetanensis
- Entamoeba histolytica
- Giardia
- Adenovirus F 40/41
- Astrovirus
- Norovirus
- Rotavirus A
- Sapovirus

**Interpretation:** A negative result should not rule-out infection in patients with a high pretest probability for gastrointestinal infection. The assay does not test for all potential infectious agents of diarrheal disease. Positive results do not distinguish between a viable/replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not contained within the panel. Results of the panel are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings.

**Reference Values:**
Negative (for all targets)

**Clinical References:**

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**Gaucher Disease, Full Gene Analysis**

**Clinical Information:** Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Reduced or absent activity of this enzyme results in accumulation of its substrate in lysosomes, interfering with cell function. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3).
In addition, there are 2 rare presentations of Gaucher disease: a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Gaucher disease demonstrates large clinical variability, even within families. Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1:18. There is a broad spectrum of disease in type 1 Gaucher disease, with some patients exhibiting severe symptoms and others very mild disease. Type 1 disease does not involve nervous system dysfunction; patients may display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. Type 2 is characterized by early-onset neurologic disease with rapid progression to death by 2 to 4 years of age. Type 3 may have early onset of symptoms, but generally a slower disease progression than type 2. Mutations in the GBA gene cause the clinical manifestations of Gaucher disease. Over 250 mutations have been reported to date. The N370S and L444P mutations have the highest prevalence in most populations. N370S is associated with type 1 Gaucher disease, and individuals with at least 1 copy of this mutation do not develop the primary neurologic disease seen in types 2 and 3. Conversely, L444P is associated with neurologic disease. For carrier screening of the general population, the recommended test is GAUP / Gaucher Disease, Mutation Analysis, GBA, which tests for the 8 most common GBA mutations. For diagnostic testing (ie, potentially affected individuals), enzyme testing (BGL / Beta-Glucosidase, Leukocytes) should be performed prior to mutation analysis. In individuals with abnormal enzyme activity and 1 or no mutations detected by a panel of common mutations, sequence analysis of the GBA gene should be utilized to detect private mutations.

**Useful For:** Confirmation of a diagnosis of Gaucher disease Carrier screening in cases where there is a family history of Gaucher disease, but an affected individual is not available for testing or disease-causing mutations have not been identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**GAUP 35436 Gaucher Disease, Mutation Analysis, GBA**

**Clinical Information:** Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of beta-glucocerebrosidase. Mutations within the beta-glucocerebrosidase gene (GBA) cause the clinical manifestations of Gaucher disease. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). Type 1 Gaucher disease occurs most frequently and is the presentation commonly found among Ashkenazi Jewish patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1 in 18. Type 1 disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. The clinical variability in type 1 disease is large, with some patients exhibiting severe disease and others very mild disease. Eight GBA mutations, including the N370S mutation found most commonly in the Ashkenazi Jewish population, are included in this test: delta 55bp, V394L, N370S, IVS2+1, 84GG, R496H, L444P, and D409H. This testing panel provides a 95% detection rate for the Ashkenazi Jewish population and up to a 60% detection rate for the non-Ashkenazi Jewish population. Alternatively, full gene sequencing is available to evaluate for mutations in all coding regions and exon/intron boundaries of the GBA gene by ordering GBAZ / Gaucher Disease, Full Gene Analysis.

**Useful For:** Confirmation of a suspected clinical diagnosis of Gaucher disease Carrier testing for
individuals of Ashkenazi Jewish ancestry or who have a family history of Gaucher disease. Prenatal
diagnosis of Gaucher disease in at-risk pregnancies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. Beutler E, Grabowski GA: Glucosylceramide lipidoses: Chpt 146: Gaucher
disease. In The Metabolic Basis of Inherited Disease. Edited by CR Scriver, AL Beaudet, WS Sly, D
and Treatment. Technology Assessment Conference Program and Abstracts, National Institutes of Health,
Registry: Demographics and disease characteristics of 1,698 patients with Gaucher Disease. Arch Int Med
2000;160:2835-2843 4. Gross SJ, Pletcher BA, Monaghan KG: Carrier screening individuals of

**FGPE 57919**

**Gelatin Porcine IgE**

**Interpretation:** Class IgE (kU/L) Comment
0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive
2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive
4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“

**Reference Values:**
<0.35 kU/L

**GELA 86326**

**Gelatin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
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<td>5</td>
<td>50.0-99.9  Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100  Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Gelsolin (GSN) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammapathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, fibrinogen alpha chain, cystatin C, lysozyme, and gelsolin. Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Gelsolin (GSN) amyloidosis (amyloidosis V) is characterized by corneal lattice dystrophy, cranial neuropathy, and skin changes. Peripheral neuropathy may be present but is typically mild. Like the other hereditary amyloidoses, it is an autosomal dominant disorder; however, homozygosity has been reported and is associated with accelerated renal disease. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnostic confirmation of amyloidosis V

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Gentamicin in Cerebrospinal Fluid (CSF)**

**Reference Values:**
Reference Range: Not Established
GENPA 37042

Gentamicin, Peak, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of ≤4 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of ≤500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 and 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of drug clearance during gentamicin therapy

Interpretation: Goal levels depend on the type of infection being treated. Peak targets are generally between 5.0 and 8.0 mcg/mL for less severe infections and 8.0 and 10.0 mcg/mL for severe infections. Prolonged exposure to peak levels exceeding 12.0 mcg/mL may lead to toxicity.

Reference Values:  
Peak: 3.0-12.0 mcg/mL  
Toxic peak: >12.0 mcg/mL


GENRA 37044

Gentamicin, Random, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of ≤4.0 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of ≤500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of serum concentration during gentamicin therapy This test is used whenever a specimen is submitted or collected without collection timing information
**Interpretation:** Goal peak concentrations levels depend on the type of infection being treated. Goal trough levels should be <2.0 mcg/mL. Peak targets are generally between 3.0 and 12.0 mcg/mL for conventional dosing. Prolonged exposure to either peak levels exceeding 12.0 mcg/mL or to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**

**Gentamicin, Peak**
- Therapeutic: 3.0-12.0 mcg/mL
- Toxic: >12.0 mcg/mL

**Gentamicin, Trough**
- Therapeutic: <2.0 mcg/mL
- Toxic: >2.0 mcg/mL

**Clinical References:**

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**Gentamicin, Trough, Serum**

**Clinical Information:** Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of < or =4.0 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of < or =500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of drug clearance during gentamicin therapy

**Interpretation:** Goal levels depend on the type of infection being treated. Goal trough levels should be <2.0 mcg/mL for conventional dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
- Therapeutic: <2.0 mcg/mL
- Toxic: >2.0 mcg/mL

**Clinical References:**

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**Geotrichum Candida (Oidium) IgE**

**Interpretation:** Class IgE (kU/L) Comment

- 0 <0.35 Below Detection
- 1 0.35 – 0.69 Low Positive
- 2 0.70 – 3.49 Moderate Positive
- 3 3.50 – 17.49 Positive
- 4 17.50 – 49.99 Strong Positive
- 5 50.00 – 99.99 Very Strong Positive
- 6 >99.99 Very Strong Positive

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Reference Values:
<0.35 kU/L

GERB
82545

Gerbil Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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GCTF
35270

Germ Cell Tumor (GCT), Isochromosome 12p, FISH, Tissue

Clinical Information: Germ cell tumors (GCT) comprise a heterogeneous group of solid neoplasms that arise in midline locations including the gonads, retroperitoneum, mediastinum, and central nervous system. GCT are categorized based upon their histologic differentiation and can be separated into 2 classes. Seminomatous GCT include seminoma of the testis, dysgerminoma of the ovaries, and germinoma of the brain. Nonseminomatous GCT include yolk sac tumor, embryonal carcinoma, choriocarcinoma, immature teratoma, and mixed forms. Due to the wide spectrum of histologic features observed in these tumors, distinction from non-GCT can be difficult. GCT are often very responsive to
chemotherapy and have a better outcome relative to histologically similar malignancies. Thus, distinguishing GCT from non-GCT is critical to providing the appropriate treatment for the patient. Gain of the short arm of chromosome 12, most commonly as an isochromosome 12p[i(12p)], is a highly nonrandom chromosomal marker seen in a significant percentage of GCT. While i(12p) is not 100% specific for GCT, the literature indicates it has diagnostic and possible therapeutic relevance for patients with these tumors. Testing of i(12p) should be concomitant with histologic evaluation, and positive results may support the diagnosis of GCT.

**Useful For:** Supporting the diagnosis of germ cell tumors when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the i(12p) probe set. A positive result is consistent with the diagnosis of a germ cell tumors (GCT). A negative result suggests that the i(12p) marker is not present, but does not exclude the diagnosis of a GCT.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FGHTL 57902**

**Ghrelin Total, Plasma**

**Reference Values:**
GHRELIN (Total): pg/mL
(Plasma)
Adult Reference Range(s)

Normal weight/control subjects: 520 - 700 pg/mL

Obese subjects prior to diet: 340 - 450 pg/mL
Levels:
8:00 am - 12:00 pm: Up to 420 pg/mL
6:00 pm: Up to 480 pg/mL

Obese subjects post induced weight loss: 450 - 600 pg/mL
Levels:
8:00 am - 12:00 pm: Up to 575 pg/mL
6:00 pm: Up to 600 pg/mL

Obese subjects post gastric-bypass surgery: Up to 120 pg/mL

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**GRW 82685**

**Giant Ragweed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Giardia Antibody, IFA**

**Reference Values:**

REFERENCE RANGE: <1:16

INTERPRETIVE CRITERIA:

<1:16  Antibody Not Detected
1:16  Equivocal; submission of a second specimen (collected 3-4 weeks after initial specimen) suggested if clinically warranted
> or = 1:32 Antibody Detected

A polyvalent conjugate (recognizing IgG, IgM and IgA) is used to detect the presence of antibodies to Giardia lamblia. A four-fold or greater increase in titer between acute and convalescent sera indicates an acute active phase. A single positive reaction represents previous exposure, since antibody titers are known to remain high for at least six months.

**Giardia Antigen, Feces**

**Clinical Information:** Giardia lamblia (also known as Giardia duodenalis, Giardia intestinalis) are flagellated protozoa that can be found contaminating natural streams, lakes, and surface water municipal reservoirs. The human host ingests them in water, food, and by the fecal-oral route. Giardia infect
primarily the small intestine causing malodorous watery diarrhea and flatulence after attaching by their ventral sucker. Malabsorption and lactose intolerance may also occur. Giardiasis is the most common intestinal parasitic infection in the United States and is a common cause of diarrhea in children (especially in day care centers), travelers, and in waterborne epidemics. Although Giardia may be detected using the microscopy-based stool parasitic exam (œova and parasite œam), up to 7 specimens may be necessary for optimal sensitivity. Instead, antigen detection using an enzyme-linked immunosorbent assay (ELISA) is a more sensitive method for detection and is therefore a preferred method for detection. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Sensitive screening for the detection of Giardia antigens present in stool specimens.

**Interpretation:** A positive enzyme-linked immunosorbent assay (ELISA) indicates the presence in a stool specimen of Giardia lamblia antigens. As per the manufacturer, the assay has a sensitivity of 96%, specificity of 97%, and a positive predictive value of 95%. Interpretation of results should be correlated with patient symptoms and clinical picture.

**Reference Values:**

Negative

**Clinical References:**

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**Giardia lamblia IgG, IgA, IgM Antibody Panel, IFA**

**Reference Values:**

**REFERENCE RANGE:**
- IgG <1:16
- IgA <1:16
- IgM <1:20

Recent or current infection by Giardia lamblia is suggested by either detection of IgM antibody or a four-fold increase in IgG and/or IgA antibody titers between acute and convalescent sera. Positive IgG and/or IgA titers without detectable IgM suggest past infection.

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**Ginger, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>&gt; or =100</td>
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</tr>
</tbody>
</table>


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**GISTP 35342 GIST Targeted Gene Panel by Next Generation Sequencing, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the United States Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. GISTP / GIST Targeted Gene Panel by Next Generation Sequencing, Tumor is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the KIT and PDGFRA genes known to be associated with gastrointestinal stromal tumors (GIST). The results of this test can be useful for assessing prognosis and guiding treatment of individuals with GIST. See Targeted Gene Regions Interrogated by Solid Tumor Targeted Cancer Gene Panel by Next Generation Sequencing in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors (GIST)

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, some individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tTG, have increased sensitivity and specificity for celiac disease. The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to test TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a study conducted at Mayo Clinic. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease.
Gliadin (Deamidated) Antibody, IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type 1 diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease,
individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tTG, have increased sensitivity and specificity for celiac disease. The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to test TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a study conducted at Mayo Clinic. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -DAGL / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

Interpretation: Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

Reference Values:
Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.


Gliadin (Deamidated) Antibody, IgG, Serum
**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy.(1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation.(2) Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population.(3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy.(1-3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient.(2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tissue transglutaminase, have increased sensitivity and specificity for celiac disease.(5,6) The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of test DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a recent study conducted at Mayo Clinic.(5) The treatment for celiac disease is maintenance of a gluten-free diet.(1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease.(1) See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDDCM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

**Interpretation:** Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet
are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease.

**Reference Values:**
Negative: <20.0 U  
Weak positive: 20.0-30.0 U  
Positive: >30.0 U  
Reference values apply to all ages.

**Clinical References:** 1. Green PH, Cellier C: Celiac disease. New Eng J Med 2007;357:1731-1743  

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**Glipizide (Glucotrol)**

**Reference Values:**
Units: ng/mL

Plasma insulin concentrations have been shown to increase only when plasma glipizide concentrations exceeded 200 ng/mL.

Toxic range has not been established.

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**Glomerular Basement Membrane Antibodies, IgG, Serum**

**Clinical Information:** Antibodies to glomerular basement membrane (GBM) antigens cause glomerulonephritis, Goodpasture syndrome (glomerulonephritis, often with rapid onset renal failure, and pulmonary hemorrhage), and, less commonly, pulmonary hemosiderosis.(1) Nephrogenic GBM antigens are associated with the noncollagenous carboxyl extension of type IV procollagen. The immunologic stimuli that elicit production of GBM antibodies are not known. There is some evidence of a genetic association with HLA-DR2. GBM antibody-mediated glomerulonephritis and Goodpasture syndrome occur with a bimodal age distribution primarily in males ages 20 to 40 and in patients older than age 50. Glomerulonephritis without pulmonary involvement is more common in the older age group, and shows a female predominance.

**Useful For:** Evaluating patients with rapid onset renal failure or pulmonary hemorrhage, as an aid in the diagnosis of Goodpasture syndrome

**Interpretation:** Positive results are consistent with Goodpasture syndrome. Glomerular basement membrane antibodies detected by immunoassay have been reported to be highly specific for Goodpasture syndrome. The sensitivity of this test approaches 87% in untreated patients with systemic disease.(1)

**Reference Values:**
<1.0 U (negative)  
> or =1.0 U (positive)  
Reference values apply to all ages.

**Clinical References:** 1. Pusey CD: Anti-glomerular basement membrane disease. Kidney Int 2003;64:1535-1550

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**Glucagon, Plasma**

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Clinical Information: Glucagon is a single-chain polypeptide of 29 amino acids that is derived from a larger precursor peptide (big plasma glucagon), which is cleaved upon secretion. The main sites of glucagon production are the hypothalamus and pancreatic alpha-islet cells. The function of hypothalamic glucagon is incompletely understood and currently no clinical disorders of hypothalamic glucagon function have been defined. Pancreatic islet glucagon is secreted in response to hypoglycemia, with resultant increases in blood glucose concentration. Glucagon’s hyperglycemic effect is produced by stimulating hepatic glycogenolysis and gluconeogenesis; it has no effect on muscle glycogen. Once blood-glucose levels have normalized, glucagon secretion ceases. Excessive glucagon secretion can lead to hyperglycemia or aggravate preexisting hyperglycemia. Excessive and inappropriate glucagon secretion can sometimes be observed in diabetes, in particular during ketoadiabetes, and can complicate management of the disorder. In rare cases, it also can occur in tumors of the pancreatic islets (glucagonoma); carcinoid tumors and other neuroendocrine neoplasms and hepatocellular carcinomas. Patients with glucagon-secreting tumors may present with classic glucagonoma syndrome, consisting of necrolytic migratory erythema, diabetes, and diarrhea, but also can have more subtle symptoms and signs. Decreased or absent glucagon response to hypoglycemia can be seen in type I diabetes (insulin-dependent diabetes) and can contribute to severe and prolonged hypoglycemic responses.

Useful For: Diagnosis and follow-up of glucagonomas and other glucagon-producing tumors
Assessing diabetic patients with problematic hyper- or hypoglycemic episodes (extremely limited utility)
Glucagon is routinely measured along with serum glucose, insulin, and C-peptide levels, during the mixed-meal test employed in the diagnostic workup of suspected postprandial hypoglycemia. However, it plays only a minor role in the interpretation of this test.

Interpretation: Elevated glucagon levels in the absence of hypoglycemia may indicate the presence of a glucagon-secreting tumor. Successful treatment of a glucagon-secreting tumor is associated with normalization of glucagon levels. Inappropriate elevations in glucagon levels in hyperglycemic type I diabetic patients indicate that paradoxical glucagon release may contribute to disease severity. This can be observed if insulin treatment is inadequate and patients are ketotic. However, glucagon measurement plays little, if any, role in the diagnostic workup of diabetic ketoacidosis, which is based on demonstrating significantly elevated plasma or serum glucose (>250 mg/dL), circulating ketones (beta-hydroxy butyrate), and acidosis (typically with increased anion gap). In diabetic patients, low glucagon levels (undetectable or in the lower quartile of the normal range) in the presence of hypoglycemia indicate impairment of hypoglycemic counter-regulation. These patients may be particularly prone to recurrent hypoglycemia. This can be a permanent problem due to islet alpha-cell destruction or other, less well understood processes (eg, autonomous neuropathy). It can also be functional, most often due to over tight blood-glucose control, and may be reversible after decreasing insulin doses.

Reference Values:
< or =6 hours: 100-650 pg/mL
1-2 days: 70-450 pg/mL
2-4 days: 100-650 pg/mL
4-14 days: declining gradually to adult levels
>14 days: < or =80 pg/mL (range based on 95% confidence limits)
Glucagon levels are inversely related to blood glucose levels at all ages. This is particularly pronounced at birth and shortly thereafter, until regular feeding patterns are established. This explains the higher levels immediately after birth, which then first fall as the glucagon release mobilizes the infant's glucose stores, then rise again as stores are depleted, finally normalizing towards adult levels as regular feeding patterns are established.

**Glucopsychosine, Blood Spot**

**Clinical Information:** Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of beta-glucosidase activity. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine). Gaucher disease is caused by mutations in the GBA gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to an asymptomatic type. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Gaucher disease type I is the most common, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system (CNS) involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease. In addition, Type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid and patients may survive into the third and fourth decade. Further subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy and/or substrate reduction therapy for types I and III. These treatment options have generally made bone marrow transplantation obsolete. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of Gaucher disease type I ranges from 1 in 30,000 to 1 in 100,000 in the general population, but is much more frequent among Ashkenazi Jews with an incidence of approximately 1 in 900. Types II and III both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (BGL / Beta-glucosidase, Leukocytes) and molecular genetic analysis of the GBA gene (GAUP / Gaucher Disease, Mutation Analysis, GBA; or GBAZ / Gaucher Disease, Full Gene Analysis). Glucopsychosine is elevated in symptomatic patients and supports a diagnosis of Gaucher disease. It may also be helpful in determining treatment response.

**Useful For:** Quantification of glucopsychosine (glucosylsphingosine) in dried blood spots supports the biochemical diagnosis of Gaucher disease. May aid in monitoring a patient’s response to treatment.

**Interpretation:** An elevation of glucopsychosine is indicative of Gaucher disease.

**Reference Values:**
Normal <47 nmol/L glucopsychosine

**Clinical References:**
of the newborn is a common presenting manifestation of GPI deficiency.

**Useful For:** A second-order test in the evaluation of individuals with chronic hemolysis

**Interpretation:** Glucose phosphate isomerase (GPI) deficiency causes a moderately severe anemia. GPI values can be 25% of normal. Increased GPI activity may be seen when young red blood cells are being produced in response to the anemia (reticulocytosis) or in the case of a newborn.

**Reference Values:**
- > or =12 months: 39.3-57.7 U/g Hb
- Reference values have not been established for patients who are <12 months of age.


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**GLUR 8412**

**Glucose, 24 Hour, Urine**

**Clinical Information:** Under normal circumstances, glucose is readily filtered by glomeruli and the filtered glucose is reabsorbed by the proximal tubule; essentially no glucose is normally excreted in the urine. However, the capacity for the proximal tubule to reabsorb glucose is limited; if the filtered load exceeds the proximal tubule's reabsorptive capacity, a portion of the filtered glucose will be excreted in the urine. Thus, elevated serum glucose concentrations (such as occur with diabetes mellitus) may result in an increase in filtered load of glucose and may overwhelm the tubules' reabsorptive capacity resulting in glucosuria. Additionally, conditions which adversely affect proximal tubule function may also result in decreased reabsorption of glucose, and increased urinary glucose concentration, even in the presence of normal plasma glucose concentrations. Some of these conditions include Fanconi syndrome, Wilson's disease, hereditary glucosuria, and interstitial nephritis. These conditions are relatively rare, and most causes for elevated urine glucose concentrations are due to elevated serum glucose levels.

**Useful For:** Limited usefulness in the screening or management of diabetes mellitus

**Interpretation:** Elevated urine glucose concentration reflects either the presence of hyperglycemia or a defect in proximal tubule function. As a screening test for diabetes mellitus, urine glucose testing has a low sensitivity (though reasonably good specificity).

**Reference Values:**
- < or =0.15 g/24 hours


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**GLBF 8343**

**Glucose, Body Fluid**

**Clinical Information:** Not available

**Useful For:** Not established

**Interpretation:** None available

**Reference Values:**
- Not applicable


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**GLURA 89115**

**Glucose, Random, Serum**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 896
Clinical Information: The most common disease related to carbohydrate metabolism is diabetes mellitus which is characterized by insufficient blood levels of active insulin. Symptoms include polyuria, abnormally elevated blood and urine glucose values, excessive thirst, constant hunger, sudden weight loss, and possibly elevated blood and urine ketones. Complications from diabetes are the third leading cause of death in the United States. There are approximately 16 million diabetics in the United States, and that number is growing. It is estimated that at least 5 million of these people have not been diagnosed. The prevalence in the population age 65 and older is 18.4%, representing 6.3 million cases. The cost of diabetes to the US economy exceeds $92 billion annually. Overproduction or excess administration of insulin causes a decrease in blood glucose to levels below normal. In severe cases, the resulting extreme hypoglycemia is followed by muscular spasm and loss of consciousness, known as insulin shock.

Useful For: Diagnosing and managing diabetes mellitus and other carbohydrate metabolism disorders including gestational diabetes, neonatal hypoglycemia, idiopathic hypoglycemia, and pancreatic islet cell carcinoma

Interpretation: Any of the following results, confirmed on a subsequent day, can be considered diagnostic for diabetes: -Fasting plasma or serum glucose ≥126 mg/dL after an 8-hour fast -2-Hour plasma or serum glucose ≥200 mg/dL during a 75-gram oral glucose tolerance test (OGTT) -Random glucose ≥200 mg/dL, plus typical symptoms Patients with "impaired" glucose regulation are those whose fasting serum or plasma glucose fall between 101 and 126 mg/dL, or whose 2-hour value on oral glucose tolerance test fall between 140 and 199 mg/dL. These patients have a markedly increased risk of developing type 2 diabetes and should be counseled for lifestyle changes and followed up with more testing. Indications for screening and testing include strong family history, marked obesity, history of babies over 9 pounds, and recurrent skin and genitourinary infections. Glucose levels < 25 mg/dL in infants <1 week are considered to be potentially life threatening; as are glucose levels < 40 mg/dL in infants >1 week. Glucose levels > 400 mg/dL are considered a critical value.

Reference Values:
0-11 months: not established
> or =1 year: 70-140 mg/dL


Glucose, Random, Urine

Clinical Information: Under normal circumstances, glucose is readily filtered by glomeruli and the filtered glucose is reabsorbed by the proximal tubule; essentially no glucose is normally excreted in the urine. However, the capacity for the proximal tubule to reabsorb glucose is limited; if the filtered load exceeds the proximal tubule’s reabsorptive capacity, a portion of the filtered glucose will be excreted in the urine. Thus, elevated serum glucose concentrations (as seen with diabetes mellitus) may result in an increase in filtered load of glucose and may overwhelm the tubules’ reabsorptive capacity resulting in glucosuria. Glucosuria occurs when the renal threshold for glucose is exceeded (typically >180 mg/dL). This is most commonly, although not exclusively, seen in diabetes. Additionally, conditions which adversely affect proximal tubule function may also result in decreased reabsorption of glucose, and increased urinary glucose concentration, even in the presence of normal plasma glucose concentrations. Some of these conditions include Fanconi syndrome, Wilson disease, hereditary glucosuria, and interstitial nephritis. These conditions are relatively rare, and most causes for elevated urine glucose concentrations are due to elevated serum glucose levels.

Useful For: An indicator of abnormal proximal tubule function Limited usefulness in the screening or management of diabetes mellitus

Interpretation: Elevated urine glucose concentration reflects either the presence of hyperglycemia or a defect in proximal tubule function. As a screening test for diabetes mellitus, urine glucose testing has a low sensitivity (though reasonably good specificity).

Reference Values:
< or =15 mg/dL
GLSF

152

Glucose, Spinal Fluid

Clinical Information: Cerebrospinal fluid (CSF) is secreted by the choroid plexuses, around the cerebral vessels, and along the walls of the ventricles of the brain, filling the ventricles and cisternae and bathing the spinal cord. CSF is reabsorbed into the blood through the arachnoid villi. CSF turnover is rapid, exchanging about 4 times per day. CSF glucose levels may be decreased due to consumption by microorganisms, impaired glucose transport, or increased glycolysis. Elevated CSF glucose levels are consistent with hyperglycemia.

Useful For: Investigating possible central nervous system infection

Interpretation: Cerebrospinal fluid (CSF) glucose levels may be decreased in any central nervous system infection, although levels are typically normal in viral meningitis, low in bacterial meningitis, and may be normal or low in fungal meningitis. CSF glucose levels are normally about 60% of blood glucose levels.

Reference Values:
Spinal fluid glucose concentration should be approximately 60% of the plasma/serum concentration and should be compared with concurrently measured plasma/serum glucose for adequate clinical interpretation.


G6PD

8368

Glucose-6-Phosphate Dehydrogenase (G-6-PD), Quantitative, Erythrocytes

Clinical Information: Hemolytic disease may be associated with deficiency of erythrocyte enzymes. The most commonly encountered is a deficiency of glucose-6-phosphate dehydrogenase (G6PD). The G6PD locus is on the X chromosome and, thus, G6PD deficiency is a sex-linked disorder. Affected males (hemizygotes) inherit the abnormal gene from their mothers who are almost always asymptomatic carriers (heterozygotes). More than 300 molecular variants of G6PD are known, and the clinical and laboratory features of G6PD deficiency vary accordingly. With some variants, there is chronic, life-long hemolysis, but much more commonly, the condition is asymptomatic and only results in susceptibility to acute hemolytic episodes, which may be triggered by some medications, ingestion of fava beans, viral, or bacterial infections. It is also associated with neonatal hyperbilirubinemia. The major G6PD variants occur in specific ethnic groups. Thus, knowledge of the ethnic background of the patient is important. G6PD deficiency has very high frequency in Southeast Asians and is the most common cause of hemolytic disease of the newborn in Southeast Asian neonates. It is also seen in persons of African and Mediterranean descent. Rasburicase therapy is contraindicated in patients with G6PD deficiency. Deficiency can be assessed by enzymatic and/or genetic assays. If deficient status can be unambiguously assigned by genotyping, that is sufficient. However, due to the limitations of genetic testing, in most cases it is necessary to perform G6PD enzyme testing to assign G6PD status (adapted from Relling et al).(1)

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia Rapid testing to assess glucose-6-phosphate dehydrogenase (G6PD) enzyme capacity prior to Rasburicase therapy

Interpretation: Abnormal values are usually 0% to 20% of normal mean. Intermediate values can occur in some genetic variants and in female carriers.

Reference Values:
> or =12 months: 8.8-13.4 U/g Hb

Reference values have not been established for patients who are <12 months of age.

G6PDB 64567

Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing

Clinical Information: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzymopathy with about 400 million people affected worldwide. It is most commonly found in populations where Plasmodium falciparum malaria is (or was) endemic, but G6PD deficiency may be present in any population. G6PD converts glucose-6-phosphate to 6-phosphoglyconolactone in the first step of the pentose phosphate pathway (PPP), this reaction also produces nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) from nicotinamide adenine dinucleotide phosphate (NADP). NADPH, through subsequent enzymatic reactions, protects erythrocytes from damage by detoxifying hydrogen peroxide and other sources of oxidative stress. G6PD is encoded by the gene G6PD, which lies on the X-chromosome. G6PD deficiency is inherited in an X-linked recessive manner; therefore, males are more commonly affected than females, but due to the high prevalence of G6PD deficiency homozygous and compound heterozygous females are not uncommon. A large number of G6PD pathogenic variants have been discovered. These variants are sub-divided into a class system based on definitions from the World Health Organization (WHO). Table 1. G6PD variant WHO class and associated G6PD deficiency phenotype WHO class Associated Clinical Presentation G6PD activity I Chronic nonspherocytic hemolytic anemia (CNSHA) <10% II Asymptomatic unless challenged <10% III Asymptomatic unless challenged 10%-60% IV None Normal With the exception of those with chronic nonspherocytic hemolytic anemia (CNSHA), individuals with G6PD deficiency are typically asymptomatic until they are challenged with an exogenous factor such as a drug, infection, or fava beans. The exogenous factor can trigger acute hemolytic anemia (AHA) in individuals with G6PD deficiency. The severity of AHA is highly variable, ranging from mild to life-threatening and can be fatal. Therefore, determining the G6PD deficiency status is recommended on the FDA label of several drugs either proven or suspected to cause AHA in patients with G6PD deficiency. For a list of drugs known to cause AHA in individuals with G6PD deficiency, see Pharmacogenomic Associations Table in Special Instructions. Preemptive genotyping allows for the identification of patients at risk for an adverse reaction to drugs known to cause AHA in those with G6PD deficiency. In most cases, genotyping provides sufficient information to avoid the use of contraindicated drugs. In some cases, including heterozygous females, the phenotyping assay is necessary to determine if such drugs should be avoided. Skewed X-inactivation in heterozygous females has been reported to result in G6PD deficiency, but the phenotyping assay is necessary to determine G6PD activity level. For more information regarding the need for G6PD enzyme activity follow-up testing to this genotyping assay, refer to the G6PD Genotyping Algorithm for Therapeutic Drug Recommendations in Special Instructions.

Useful For: Genetic test for individuals at high risk for G6PD deficiency; for initial or time-sensitive screening for G6PD deficiency, refer to phenotyping enzyme assay G6PD / Glucose-6-Phosphate Dehydrogenase (G-6-PD), Quantitative, Erythrocytes Aiding in the diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency Determining G6PD deficiency status in individuals with inconclusive or unexpected phenotyping results Differentiation of heterozygous females with skewed X-inactivation from homozygous and compound heterozygous females Definitive diagnosis of carrier status in females Evaluation of neonates (particularly males) with unexplained jaundice Identifying individuals at risk of drug-induced acute hemolytic anemia (AHA) related to G6PD deficiency

Interpretation: All detected alterations will be evaluated according to the latest American College of Medical Genetics recommendations.(1) Variants will be classified based on known, predicted, or possible effect on gene pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


**FGAE**

**Glutamic Acid (MSG) IgE**

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Conc IU/mL</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>&lt;0.05</td>
<td>Negative</td>
</tr>
<tr>
<td>0/I</td>
<td>0.05 â€“ 0.08</td>
<td>Equivocal</td>
</tr>
<tr>
<td>I</td>
<td>0.08 â€“ 0.15</td>
<td>Positive</td>
</tr>
<tr>
<td>II</td>
<td>0.15 â€“ 0.50</td>
<td>with</td>
</tr>
<tr>
<td>III</td>
<td>0.50 â€“ 2.50</td>
<td>Increasing</td>
</tr>
<tr>
<td>IV</td>
<td>2.50 â€“ 12.50</td>
<td>Antibody</td>
</tr>
<tr>
<td>V</td>
<td>12.50 â€“ 62.50</td>
<td>Concentration</td>
</tr>
<tr>
<td>VI</td>
<td>&gt;62.50</td>
<td></td>
</tr>
</tbody>
</table>

**GD65S**

**Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum**

**Clinical Information:** Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Antibodies directed against the 65-kd isoform of GAD (GAD65) are seen in a variety of autoimmune neurologic disorders including stiff-man (Moersch-Woltman) syndrome, autoimmune cerebellitis, brain stem encephalitis, seizure disorders, neuromyelitis optica and other myelopathies, myasthenia gravis, Lambert-Eaton syndrome, and dysautonomia. GAD65 antibody is also the major pancreatic islet antibody and an important serological marker of predisposition to type 1 diabetes. GAD65 autoantibody also serves as a marker of predisposition to other autoimmune disease that occur with type 1 diabetes, including thyroid disease (eg, thyrotoxicosis, Grave disease, Hashimoto thyroiditis, hypothyroidism), pernicious anemia, premature ovarian failure, Addison disease, (idiopathic adrenocortical failure) and vitiligo.

**Useful For:** Assessing susceptibility to autoimmune (type 1, insulin-dependent) diabetes mellitus and related endocrine disorders (eg, thyroiditis and pernicious anemia). Titers generally < or =0.02 nmol/L. A second islet cell antibody (IA-2) is more predictive for development of type 1 diabetes, but less frequent than glutamic acid decarboxylase (GAD65) antibody amongst diabetic patients. Insulin autoantibodies also serve as a marker of susceptibility to type 1 diabetes. Distinguishing between patients with type 1 and type 2 diabetes. Assays for IA-2, insulin, gastric parietal cell, thyroglobulin, and thyroid peroxidase antibodies complement GAD65 antibody in this context; titers generally < or =0.02 nmol/L. Confirming a diagnosis of stiff-man syndrome, autoimmune encephalitis, cerebellitis, brain stem encephalitis, myelitis; titers generally > or =0.03 nmol/L. Confirming susceptibility to organ-specific neurological disorders (eg, myasthenia gravis, Lambert-Eaton syndrome); titers generally < or =0.02 nmol/L

**Interpretation:** High titers (> or =0.02 nmol/L) are found in classic stiff-man syndrome (93% positive) and in related autoimmune neurologic disorders (eg, acquired cerebellar ataxia, some acquired nonparaneoplastic encephalomyelopathies). Diabetic patients with polyendocrine disorders also generally have glutamic acid decarboxylase (GAD65) antibody values > or =0.02 nmol/L. Values in patients who have type 1 diabetes without a polyendocrine or autoimmune neurologic syndrome are usually < or =0.02
nmol/L. Low titers (0.03-19.9 nmol/L) are detectable in the serum of approximately 80% of type 1 diabetic patients. Conversely, low titers are detectable in the serum of <5% of type 2 diabetic patients. Low titers are found in approximately 25% of patients with myasthenia gravis, Lambert-Eaton syndrome, and rarer autoimmune neurological disorders. Eight percent of healthy Olmsted County residents over age 50 have low-positive values. These are not false positive; the antibodies are inhibited by unlabeled GAD65 antigen and are accompanied in at least 50% of cases by related organ-specific autoantibodies. Values > or =0.03 nmol/L are consistent with susceptibility to autoimmune (type 1) diabetes and related endocrine disorders (thyroiditis and pernicious anemia).

Reference Values:
< or =0.02 nmol/L.
Reference values apply to all ages.


**Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid**

**Clinical Information:** Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Serum antibodies directed against the 65-kd isoform of GAD (GAD65) are detected in heightened frequency in a variety of autoimmune neurologic disorders, including stiff-man (Moersch-Woltman) syndrome, autoimmune cerebellitis, some idiopathically acquired epilepsies, some rare acquired encephalomyelopathies with and without neoplasia, and in myasthenia gravis and Lambert-Eaton myasthenic syndrome. GAD65 antibodies account for the majority of clinically-recognized pancreatic islet cell antibodies, and are an important serological marker of predisposition to type 1 (insulin-dependent) diabetes. GAD65 autoantibodies also serve as a marker of predisposition to autoimmune disorders that commonly or sometimes coexist with type 1 diabetes, including autoimmune thyroid disease (eg, thyrotoxicosis, Graves' disease, Hashimoto's thyroiditis, hypothyroidism), pernicious anemia, premature ovarian failure, Addison's disease (idiopathic adrenocortical failure), and vitiligo. GAD65 antibodies are found in the serum of approximately 8% of healthy subjects older than age 50, usually in low titer, but often accompanied by related "thyrogastric" autoantibodies.

**Useful For:** Possible use in evaluating patients with stiff-man syndrome, autoimmune cerebellitis and other acquired central nervous system disorders affecting gabaminergic neurotransmission. Clinical utility remains to be determined.

**Interpretation:** Intrathecal synthesis of GAD65 antibody has been demonstrated in patients with stiff-man syndrome, but cerebrospinal fluid (CSF) values are log orders lower than serum. We have not determined the frequency of GAD65 antibodies in CSF of patients with various diagnoses.

**Reference Values:**
< or =0.02 nmol/L.

Gluten IgG

**Interpretation:** mcg/mL of IgG
- **Lower Limit of Quantitation:** 2.0
- **Upper Limit of Quantitation:** **200

**Reference Values:**
- < 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Gluten, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.
**TGGB 63445**

**Glycerol-Corrected Triglycerides, Serum**

**Clinical Information:** Triglycerides are esters of glycerol with 3 long-chain fatty acids. Increased plasma triglyceride concentrations are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (eg, prednisone). See Lipids and Lipoproteins in Blood Plasma in Special Instructions. Traditional, nonglycerol-blanked methods for measuring triglycerides break down plasma and serum triglycerides into glycerol and fatty acids. The glycerol is then measured in an enzymatic colorimetric assay. Consequently, patients with elevated free glycerol in circulation will have a falsely elevated triglyceride concentration, pseudohypertriglyceridemia, when using a nonglycerol-blanked triglyceride assay. Glycerol is an intermediate in the conversion of glucose to lipids and serves as the precursor for triglyceride and other glycerolipids. Patients with type 2 diabetes mellitus, hyperthyroidism, those who are obese, or those receiving oral or parenteral supplementation with glycerol may have slightly higher free glycerol in circulation, however this increase is unlikely to affect triglyceride result interpretation. Glycerol kinase deficiency (GKD) is an X-linked genetic condition leading to impaired function of glycerol kinase (GK), the primary regulator of glycerol entry into metabolic pathways. Insufficient GK activity leads to extreme elevations in plasma glycerol concentrations (ie, hyperglycerolemia) and glyceroluria. Patients with GKD may be placed on a glycerol-restricted diet and instructed to avoid prolonged periods of fasting. GKD is divided into 3 clinical forms: -Complex GKD involves mutations in the GK locus and 2 others (adrenal hypoplasia congenital: AHC and Duchenne muscular dystrophy: DMD) on Xp21 and manifests in infants. -Juvenile GKD is associated with metabolic and central nervous system instability and deterioration. Juvenile GKD usually presents in the early years of life as repeated vomiting, acidemia, and central nervous system depression. - Adult GKD is mainly benign with detection usually found incidentally by pseudohypertriglyceridemia.

**Useful For:** Evaluation of pseudohypertriglyceridemia for possible glycerol kinase deficiency
Evaluation of triglyceride as a cardiovascular risk factor in individuals with elevated cholesterol values

**Interpretation:** Patients with glycerol kinase deficiency typically have serum free glycerol concentrations greater than 10 fold above normal.

**Reference Values:**

TRIGLYCERIDE, TOTAL and CORRECTED

The National Cholesterol Education Program (NCEP) has set the following guidelines in adults ages 18 and up:

- Normal: <150 mg/dL
- Borderline high: 150-199 mg/dL
- High: 200-499 mg/dL
- Very high: > or =500 mg/dL

The National Cholesterol Education Program (NCEP) and National Health and Nutrition Examination Survey (NHANES) has set the following guidelines in children ages <2:

- <2 years: Reference values have not been established for patients who are <24 months of age.

2-9 years:

- Acceptable: <75 mg/dL
- Borderline high: 75-99 mg/dL
- High: > or =100 mg/dL

10-17 years:

- Normal: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL

GLYCEROL, CALCULATED
<18 years: Reference values have not been established for patients who are <18 years of age.
>18 years: 40-370 mcmol/L

Clinical References:

FGLMA 91742

GlycoMark
Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 17 y</td>
<td>Not established</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Males:</td>
<td>10.7 - 32.0</td>
</tr>
<tr>
<td>Adult Females:</td>
<td>6.8 - 29.3</td>
</tr>
</tbody>
</table>

Glycemic control goal for diabetic patients: >10

GlycoMark is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.

1. 1, 5-AG blood levels can be affected by clinical conditions or medications.

Test Performed By: Esoterix Endocrinology
4301 Lost Hills Road
Calabasas Hills, CA 91301

GDOM 82847

Glycyphagus domesticus, IgE
Clinical Information:
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For:
Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Interpretation</th>
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**UVEAL 35567**

**GNAQ/GNA11 Mutation Analysis, Uveal Melanoma**

**Clinical Information:** The GNAQ and GNA11 codon 209 mutations in exon 5 are the most common genetic alterations in uveal melanoma, occurring in around 80% of uveal melanoma tumors. Additionally, these mutations occur almost exclusively in uveal melanomas and blue nevi. Detection of the codon 209 mutations can help in the diagnosis of uveal melanoma cases, as well as aid in knowledge of prognosis and possible therapeutic approaches.

**Useful For:** Aiding in the diagnosis of uveal melanoma and targeting therapeutic approaches

**Interpretation:** An interpretive report will be provided.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


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**GNPTZ 35442**

**GNPTAB Gene, Full Gene Analysis**

**Clinical Information:** N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits (GNPTAB)-related mucolipidoses are progressive lysosomal storage diseases traditionally classified as mucolipidosis II and mucolipidosis III based upon their severity and disease onset. These conditions have substantial clinical overlap and mutation testing can aid the diagnosis. Mucolipidosis II alpha/beta (ML II
alpha/beta or I-cell disease) is a progressive inborn error of metabolism with clinical onset at birth and fatal outcome most often in early childhood. Postnatal growth is limited and often ceases in the second year of life; contractures develop in all large joints. The skin is thickened, facial features are coarse, and gingiva are hypertrophic. Orthopedic abnormalities present at birth may include thoracic deformity, kyphosis, clubfeet, deformed long bones, and hip dislocation. There is often cardiac involvement, most commonly thickening and insufficiency of the mitral valve and, less frequently, the aortic valve. Progressive mucosal thickening narrows the airways and gradual stiffening of the thoracic cage contributes to respiratory insufficiency, the most common cause of death. Mucolipidosis III alpha/beta (ML III alpha/beta or pseudo-Hurler polydystrophy) is a slowly progressive disorder with clinical onset at approximately 3 years of age. It is characterized by a slow growth rate and subnormal stature; radiographic evidence of mild-to-moderate dysostosis multiplex; joint stiffness and pain initially in the shoulders, hips, and fingers; gradual mild coarsening of facial features; and normal to mildly impaired cognitive development. If present, organomegaly is mild. Pain from osteoporosis that is clinically and radiologically apparent in childhood becomes more severe from adolescence. Cardiorespiratory complications (restrictive lung disease, thickening and insufficiency of the mitral and aortic valves, left and/or right ventricular hypertrophy) are common causes of death, typically in early to middle adulthood. ML II/ML III alpha/beta are inherited in an autosomal recessive manner. Both disorders have been reported from nearly all parts of the world and the overall carrier rate ranges between 1 in 158 and 1 in 316. GNPTAB is the gene in which mutations are most often known to cause ML II/ML III alpha/beta. Bidirectional sequencing of the entire GNPTAB coding region detects 2 disease-causing mutations in more than 95% of individuals with ML II/MLIII alpha/beta. This gene encodes 2 of 3 subunits (alpha/beta) of the heterohexameric enzyme, N-acetylglucosamine-1-phosphotransferase. In the absence of this enzyme, a mannose 6-phosphate (M6P) recognition marker is not added to lysosomal hydrolases and other glycoproteins. This leads to disruption of acid hydrolases transport to the lysosome. Formation of the M6P recognition marker on lysosomal hydrolases is significantly reduced in ML III alpha/beta, and nearly or totally absent in ML II alpha/beta. To confirm or establish the diagnosis in a proband requires a combination of clinical evaluation and laboratory testing. The use of the following diagnostic testing is recommended: Identification of characteristic clinical and radiographic findings, assay of oligosaccharides in urine, assay of several acid hydrolases in plasma, sequence analysis of GNPTAB. The activity of nearly all lysosomal hydrolases in plasma and other body fluids is higher in individuals affected with ML II alpha/beta (5- to 20-fold) and ML III alpha/beta (up to 10-fold) than in normal controls. ML II/ML III alpha/beta is diagnosed by assay of N-acetylglucosamine-1-phosphotransferase in skin fibroblasts. Demonstration of nearly complete inactivity (<1%) of the enzyme confirms the diagnosis of ML II alpha/beta, whereas significant deficiency (1%-10% of normal) of this enzyme is suggestive of the diagnosis of ML III alpha/beta. Urinary excretion of oligosaccharides is often excessive. Prior to molecular analysis, the delineation of ML II alpha/beta from ML III alpha/beta depended solely on clinical criteria including age of onset, rate of progression, and overall severity. Molecular genetic studies reveal a genotype-phenotype correlation supporting the clinical distinction between ML II alpha/beta and ML III alpha/beta. Mutations that completely inactivate the phosphotransferase consistently result in ML II alpha/beta, irrespective of their location within the gene. Mutations with less adverse effect on this enzyme activity usually result in ML III alpha/beta or occasionally in intermediate phenotypes.(1,2)

**Useful For:** Molecular diagnosis or carrier status of mucolipidosis II alpha/beta and mucolipidosis III alpha/beta in conjunction with identification of characteristic clinical, radiographic, and biochemical findings, and genetic counseling for family members

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Goat Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Goat's Milk, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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FGNRH 90165  
Gonadotropin Releasing Hormone (Gn-RH)

Clinical Information: Gonadotropin-Releasing Hormone (Gn-RH), also known as Luteinizing Hormone-Releasing Hormone (LH-RH), is a Decapeptide secreted pulsatily from the hypothalamus. It stimulates the release of the Gonadotropins - Luteinizing Hormone and Follicle Stimulating Hormone - exerting a stronger effect on Luteinizing Hormone. Testosterone and Estradiol, whose release is stimulated by the Gonadotropins, exert a negative feedback control on LH-RH both at the hypothalamic site and by decreasing pituitary receptor binding. LH-RH levels are low in patients with hypothalamic hypogonadism differentiating them from the high levels usually found in primary hypopituitary hypogonadism. Accentuation of the LH-RH pulse occurs at the onset of puberty triggering the release of LH and FSH required in pubertal development. LH-RH is stimulated by Epinephrine and suppressed by Dopamine and opiates. LH-RH and some of its agonists are frequently used to induce ovulation.

Reference Values:
Adult Reference Range(s):

Males:  4.0 - 8.0 pg/mL
Females:  2.0 - 10.0 pg/mL

GOOS 82714  
Goose Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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FGMD 57954
Grain Dust Elevator IgE (Equal parts: Corn mill, Peanut, Sorghum, Soybean, Rye mill, Rice, Oat grain, Milo and Wheat)

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

GWEE 82378
Grain Weevil, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflamatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**GRAM 8078**

**Gram Stain**

**Clinical Information:** The Gram stain is a general stain used extensively in microbiology for the preliminary differentiation of microbiological organisms. The Gram stain is one of the simplest, least expensive, and most useful of the rapid methods used to identify and classify bacteria. The Gram stain is used to provide preliminary information concerning the type of organisms present directly from clinical specimens or from growth on culture plates. This stain is used to identify the presence of microorganisms in normally sterile body fluids (cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid). It is also used to screen sputum specimens to establish acceptability for bacterial culture (<25 squamous epithelial cells per field is considered an acceptable specimen for culture) and may reveal the causative organism in bacterial pneumonia.

**Useful For:** Identifying microorganisms in normally sterile body fluids Screening sputum specimens for acceptability for bacterial culture Guiding initial antimicrobial therapy

**Interpretation:** During the staining process, the crystal violet and iodine form a complex within the heat fixed cell. In gram-negative organisms, this complex is readily washed out by the acetone-alcohol. They appear red because they retain only the safranin dye (counterstain). Gram-positive organisms retain the crystal violet-iodine complex after decolorization and remain purple.

**Reference Values:** No organisms seen or descriptive report of observations.


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**GSBV 61565**

**Gram Stain for Bacterial Vaginosis**

**Clinical Information:** Bacterial vaginosis is so-named because bacteria are the cause and an associated inflammatory response is lacking. It results in an increase in thin, gray, homogeneous vaginal discharge and vaginal malodor and is caused by a change in the vaginal flora. Bacterial vaginosis is a synergistic polymicrobial infection not caused by 1 specific organism. The standard scoring system termed the "Nugent score" is a technique for assessing bacterial vaginosis using microscopic examination of a Gram-stained smear of vaginal discharge.
Useful For: Providing evidence to support the diagnosis of bacterial vaginosis

Interpretation: Assessment of a Gram-stained slide using the Nugent score has replaced culture as the preferred test to diagnose bacterial vaginosis.(1) While Gardnerella is the most common anaerobe found in bacterial vaginosis, other anaerobic organisms are often present along with a decrease in the amount of "usual flora" (eg, Lactobacillus species). This system uses a 0- to 4-point scale to calculate the weighted sum of the following 3 bacterial morphotypes: Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus species. A total score of >6 is considered abnormal, a total score of 4 to 6 is considered a transitional stage, and a total score of 0 to 3 is considered normal. Clue cells and yeast are also reported, if present.

Reference Values:
One of the 3 following reports dependent on the weighted sum balance of Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus species:
1. Consistent with normal bacterial vaginal flora.
2. Altered vaginal flora not consistent with bacterial vaginosis. This frequently represents a transitional stage. If signs and/or symptoms persist, repeat testing is warranted.
3. Consistent with bacterial vaginosis.

Clinical References: 1. CAP Microbiology checklist: Bacterial Vaginosis - Evaluation of a criterion-based Gram stain is used for the microscopic diagnosis of bacterial vaginosis. 2011

Granulocyte Antibodies, Serum

Clinical Information: Granulocyte antibodies are induced by pregnancy or prior transfusion and are associated with febrile, nonhemolytic transfusion reactions. Patients who have been immunized by previous transfusions, pregnancies, or allografts frequently experience febrile, nonhemolytic transfusion reactions which must be distinguished from hemolysis before further transfusions can be safely administered. Granulocyte antibodies may also be present in autoimmune neutropenia.

Useful For: The work-up of individuals having febrile, nonhemolytic transfusion reactions The detection of individuals with autoimmune neutropenia

Interpretation: A positive result in an individual being worked up for a febrile transfusion reaction indicates the need for leukocyte-poor (filtered) red blood cells. This test cannot distinguish between allo- and autoantibodies

Reference Values:
Not applicable


Grape IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Grape, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Grapefruit, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
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GRAS2 Grass Panel # 2

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>Positive</td>
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<td>4</td>
<td>17.5-49.9</td>
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<td>&gt; or =100</td>
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**GRAS3 81708**

**Grass Panel # 3**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**GRFE 82365**

**Greek Fennel, IgE**

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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Green Coffee Bean, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders

**Grey Alder, IgE**

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**GRHPZ**

**GRHPR Gene, Full Gene Analysis**

**Clinical Information:** Primary hyperoxaluria type 2 (PH2) is a hereditary disorder of glyoxylate metabolism caused by deficiency of the hepatic enzyme glyoxylate reductase/hydroxypruvrate reductase (GRHPR). Absence of GRHPR activity results in excess oxalate and usually L-glycerate excreted in the urine leading to nephrolithiasis (kidney stones) and sometimes renal failure. Onset of PH2 is typically in childhood or adolescence with symptoms related to kidney stones. In some cases, kidney failure may be the initial presenting feature. Nephrocalcinosis, as seen by renal ultrasound, is observed less frequently in individuals with PH2 than primary hyperoxaluria type 1 (PH1). End-stage renal disease (ESRD) is also less common and of later onset than PH1; however, once ESRD develops, oxalate deposition in other organs such as bone, retina, and myocardium can occur. While the exact prevalence and incidence of PH2 are not known, it is thought that PH2 is less common than PH1, which has an estimated prevalence rate of 1 to 3 per million population and an incidence of 0.1 per million/year. Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate in a timed, 24-hour urine collection is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, Urine). In very young children (incapable of performing a timed collection), random urine oxalate to creatinine ratios may be used for determination of oxalate excretion. In patients with reduced kidney function, POXA / Oxalate, Plasma is also recommended. Urinary excretion of oxalate of >1.0 mmol/1.73 m(2)/24 hours is strongly suggestive of, but not diagnostic, for primary hyperoxaluria as there are other forms of inherited hyperoxaluria (PH1 and non-PH1/PH2) and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycerate in the presence of hyperoxaluria is suggestive of PH2. Caution is warranted in interpretation of urine oxalate excretion in patients with reduced kidney function as urine oxalate concentrations may be lower due to reduced glomerular filtration rate. Historically, the diagnosis of PH2 was confirmed by GRHPR enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases. PH2 is inherited as an autosomal recessive disorder caused by mutations in the GRHPR gene, which encodes the enzyme GRHPR. Two common GRHPR mutations have been identified: c.103delG and c.403_404+2delAAGT. These mutations account for about one-third of the mutant alleles described in the Northern European Caucasian population and about 15% in the Asian population. Direct sequencing of the GRHPR gene will identify these 2 mutations as well as other less common or novel mutations associated with PH2.

**Useful For:** Confirming a diagnosis of primary hyperoxaluria type 2 (PH2) Carrier testing for individuals with a family history of PH2 in the absence of known mutations in the family

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

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1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.
An interpretive report will be provided.


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**Group A Streptococcus (Streptococcus pyogenes) Culture**

**Clinical Information:** Streptococcus pyogenes (group A streptococcus) is a common cause of pharyngitis and skin and soft tissue infection. In children, Streptococcus pyogenes can cause perianal infection. The classic presentation is a well-demarcated rash around the anus, with itching, rectal pain, and occasionally, blood-streaked stools. Untreated, painful defecation, toilet avoidance, and constipation may persist for months, until effective treatment is administered. Anal fissures may ensue. A swab of the affected area may be submitted for Streptococcus pyogenes culture to confirm the diagnosis. Health care workers may transmit Streptococcus pyogenes to their patients (eg, in the postsurgical setting) leading to outbreaks of invasive disease. Screening of health care workers or other patients for Streptococcus pyogenes may be requested by Infection Prevention and Control as part of an investigation of a potential nosocomial case (or cases). Isolates may be typed to assess strain relatedness.

**Useful For:** Diagnosis of perianal cellulitis or for screening of patients and health care workers for Streptococcus pyogenes for the purpose of investigating possible nosocomial transmission

**Interpretation:** Positive cultures are reported out as Streptococcus pyogenes.

**Reference Values:** Negative


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**Group B Streptococcus (Streptococcus agalactiae) Culture**

**Clinical Information:** Streptococcus agalactiae (group B streptococcus) is a cause of morbidity and mortality among infants. Infections occurring within the first week of life are considered early-onset; those occurring in infants >1 week of age are considered late-onset. Maternal vaginal or rectal colonization with Streptococcus agalactiae is a risk factor for early-onset disease in infants. Ten to 30% of pregnant women are vaginally or rectally colonized with Streptococcus agalactiae and may transmit the organism to their infant during labor and delivery. The Centers for Disease Control and Prevention recommends screening for colonization with Streptococcus agalactiae at 35 to 37 weeks gestation as a guide for intrapartum antibiotic prophylaxis to decrease the risk of infection with Streptococcus agalactiae in the infant.

**Useful For:** Screening for maternal colonization with Streptococcus agalactiae at 35 to 37 weeks gestation as a guide for intrapartum antibiotic prophylaxis to decrease the risk of infection by Streptococcus agalactiae in the infant

**Interpretation:** Positive cultures are reported out as Streptococcus agalactiae.

**Reference Values:** Negative

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Current as of July 8, 2016 11:28 am CDT

**FGRPR**

**Grouper IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**ABO_M**

**Grouping and Rh, Blood**

**Clinical Information:** The ABO and Rh typing indicates the presence of specific red cell antigens of 2 of the various blood group systems.

**Useful For:** Selecting compatible blood products for transfusion therapy

**Reference Values:**
Not applicable

**GDF15**

**Growth Differentiation Factor 15 (GDF15), Plasma**

**Clinical Information:** Mitochondria perform many important metabolic functions, the most vital being the production of energy in the form of adenosine triphosphate (ATP) through the electron-transport chain and the oxidative phosphorylation system, which consists of 5 complexes (Complex I-V). Each of these complexes consists of between 4 and 46 subunits encoded by both nuclear and mitochondrial DNA. Mitochondrial diseases are caused by defects in any of the relevant metabolic pathways and have an estimated prevalence of 1:8,500. Mitochondrial diseases are varied, including mitochondrial DNA deletion syndromes such as Kearns-Sayre syndrome (KSS), mitochondrial depletion syndromes such as those caused by mutations in TK2 and SUCLA2 or POLG and C10orf2, and mitochondrial point mutation syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), as well as others. The clinical features of mitochondrial diseases vary widely, but they can include lactic acidosis, myopathy, ophthalmoplegia, ptosis, cardiomyopathy, sensorineural hearing loss, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalomyopathy, seizures, and stroke-like episodes. A diagnostic workup for a mitochondrial disorder may demonstrate elevations of the lactate-to-pyruvate ratio (LAA / Lactate, Plasma and PYR / Pyruvic Acid, Blood) and an elevated growth differentiation factor 15 (GDF15) level. GDF15 is a protein of the transforming growth factor beta superfamily. GDF15 is overexpressed in muscle and serum in patients with various types of mitochondrial diseases, including those with mitochondrial deletion, depletion, and point mutation syndromes. Therefore, increased levels of GDF15 can indicate the need for further investigations including molecular studies and muscle biopsy to confirm the presence of a possible neuromuscular mitochondrial disease.

**Useful For:** As a circulating biomarker in myopathy-related mitochondrial disease as well as other conditions

**Interpretation:** Abnormal results may be suggestive of mitochondrial disease alongside clinical findings. Additional workup is indicated.

**Reference Values:**
3 months* and older: < or =750 pg/mL
*This test is not recommended for infants <3 months of age due to the high levels of GDF15 contributed from the placenta during pregnancy.


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**FGHBP**

**Growth Hormone Binding Protein (GHBP)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1y</td>
<td>&lt;125-762</td>
</tr>
<tr>
<td>2-9y</td>
<td>267-1638</td>
</tr>
<tr>
<td>10-14y</td>
<td>431-1892</td>
</tr>
<tr>
<td>20-50y</td>
<td>686-2019</td>
</tr>
</tbody>
</table>

Test Performed By: Esoterix Endocrinology

4301 Lost Hills Road
Calabasas Hills, CA 91301

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**HGH**

**Growth Hormone, Serum**

**Clinical Information:** The anterior pituitary secretes human growth hormone (hGH) in response to exercise, deep sleep, hypoglycemia, and protein ingestion. hGH stimulates hepatic insulin-like growth factor-1 and mobilizes fatty acids from fat deposits to the liver. Hyposcretion of hGH causes dwarfism in children. Hypersecretion causes gigantism in children or acromegaly in adults. Because hGH levels in normal and diseased populations overlap, hGH suppression and stimulation tests are needed to evaluate conditions of hGH excess and deficiency; random hGH levels are inadequate.

**Useful For:** Diagnosis of acromegaly and assessment of treatment efficacy (in conjunction with glucose suppression test) Diagnosis of human growth hormone deficiency (in conjunction with growth hormone stimulation test)

**Interpretation:** Acromegaly: For suppression testing, normal subjects have a nadir growth hormone (GH) concentration of <0.3 ng/mL after ingestion of a 75-gram glucose dose. Patients with acromegaly fail to show normal suppression. Using the Access ultrasensitive hGH assay, a cutoff of 0.53 ng/mL for nadir GH was found to most accurately differentiate patients with acromegaly in remission from active disease with a sensitivity of 97% (95% CI, 83%-100%) and a specificity of 100% (95% CI, 82%-100%).(1) Deficiency: A normal response following stimulation tests is a peak GH concentration >5 ng/mL in children and >4 ng/mL in adults. For children, some experts consider GH values between 5 ng/mL and 8 ng/mL equivocal and only GH peak values >8 ng/mL as truly normal. Low levels, particularly under stimulation, indicate human growth hormone deficiency.

**Reference Values:**

Adults

- Males: 0.01-0.97 ng/mL
- Females: 0.01-3.61 ng/mL

Reference intervals have not been formally verified in-house for pediatric and adolescent patients. The published literature indicates that reference intervals for adult, pediatric, and adolescent patients are comparable.

Growth Hormone-Releasing Hormone (GH-RH)

Clinical Information: Growth Hormone Releasing Hormone is a 44 amino acid peptide produced primarily by the hypothalamus. It is a neurohumoral control for adenohypophyseal secretion of Growth Hormone. Other hypothalamic hormones have a stimulatory effect on pituitary hormones, but Growth Hormone Releasing Hormone has no known effect on other pituitary hormones. Somatostatin is the inhibitory counterpart of Growth Hormone Releasing Hormone. Growth Hormone Releasing Hormone has structural similarities with the Secretin-Glucagon family of gastrointestinal hormones. Growth Hormone Releasing Hormone has been isolated from pancreatic islet cells and various cancer tumor cells.

Reference Values:
Levels of IR-GH-RH
- Baseline range: 5 - 18 pg/mL
- Levels in GH-RH Dysfunction:
  - Patients with acromegaly: up to 200 pg/mL
  - Patients with small cell lung carcinoma: up to 50 pg/mL
  - GH-RH secreting tumors: 200 -10,000 pg/mL

This test was performed using a kit that has not been cleared or approved by the FDA and is designated as research use only.

Guar Gum, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Guava, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**Guinea Pig Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Gum Arabic, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;99.99</td>
<td>Very Strong Positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Gum Carageenan IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.4 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**Gum Xanthan IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.4 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L
0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

**FHACK**

**Hackberry (Celtis occidentalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >100 Very High Positive

Reference Values:
<0.35 kU/L

**FHADE**

**Haddock (Melanogrammus aeglefinus) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal 1 0.35 – 0.69 Low Positive 2 0.70 – 3.4 Moderate Positive 3 3.5 – 17.4 High Positive 4 17.5 – 49.9 Very High Positive 5 50.0 – 99.9 Very High Positive 6 >100 Very High Positive

Reference Values:
<0.35 kU/L

**HIBS**

**Haemophilus influenzae Type B Antibody, IgG, Serum**

**Clinical Information:** Haemophilus influenzae type B (HIB) is an encapsulated gram-negative cocco-bacillary bacterium that can cause devastating disease in young children including meningitis, bacteremia, cellulitis, epiglottitis, pneumonia, and septic arthritis. One of the great advances in modern medicine has been the development of an effective vaccine against HIB. A patient's immunological response to HIB vaccine can be determined by measuring anti-HIB IgG antibody using this EIA technique.

**Useful For:** Assessing a patient's immunological (IgG) response to Haemophilus influenzae type B (HIB) vaccine Assessing immunity against HIB Aiding in the evaluation of immunodeficiency

**Interpretation:** An anti-Haemophilus influenzae type B (HIB) IgG antibody concentration of 0.15 mg/L is generally accepted as the minimum level for protection at a given time; however, it does not confer long-term protection. A study from Finland suggested that the optimum protective level is 1.0 mg/L postimmunization.(1) Furthermore, studies have shown that the response to HIB vaccine is age-related. By testing pre- and postvaccination patient serum specimens, this test may be used to aid diagnosis of immunodeficiency.

**Reference Values:**
> or =0.15 mg/L


**HAKE**

**Hake, Fish, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE...
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Halibut IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Halibut, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**HALO 80339**

**Haloperidol, Serum**

**Clinical Information:** Haloperidol (Haldol) is a member of the butyrophenone class of neuroleptic drugs used to treat psychotic disorders (eg, schizophrenia). It is also used to control the tics and verbal utterances associated with Tourette's syndrome and in the management of intensely hyperexcitable children who fail to respond to other treatment modalities. The daily recommended oral dose for patients with moderate symptoms is 0.5 to 2.0 mg; for patients with severe symptoms, 3 to 5 mg may be used. However, some patients will respond only at significantly higher doses. Haloperidol is metabolized in the liver to reduced haloperidol, its major metabolite.(1,2) Use of haloperidol is associated with significant toxic side effects, the most serious of which include tardive dyskinesia which can be irreversible, extrapyramidal reactions with Parkinson-like symptoms, and neuroleptic malignant syndrome. Less serious side effects can include hypotension, anticholinergic effects (blurred vision, dry mouth, constipation, urinary retention), and sedation. The risk of developing serious, irreversible side effects seems to increase with increasing cumulative doses over time.(1,3)

**Useful For:** Optimizing dosage Monitoring compliance Assessing toxicity
Interpretation: Studies show a strong relationship between dose and serum concentration (4); however, there is a modest relationship of clinical response or risk of developing long-term side effects to either dose or serum concentration. A therapeutic window exists for haloperidol; patients who respond at serum concentrations between 5 to 16 ng/mL show no additional improvement at concentrations >16 to 20 ng/mL.(3,5) Some patients may respond at concentrations <5 ng/mL, and others may require concentrations significantly >20 ng/mL before an adequate response is attained. Because of such inter-individual variation, the serum concentration should only be used as 1 factor in determining the appropriate dose and must be interpreted in conjunction with the clinical status. Although the metabolite, reduced haloperidol, has minimal pharmacologic activity, evidence has been presented suggesting that an elevated ratio of reduced haloperidol-to-haloperidol (ie, >5) is predictive of a poor clinical response.(3,6) A reduced haloperidol-to-haloperidol ratio <0.5 indicates noncompliance; the metabolite does not accumulate except during steady-state conditions.

Reference Values:
HALOPERIDOL
5-16 ng/mL

REDUCED HALOPERIDOL
10-80 ng/mL


Hamster Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

FHAN 90405

Hantavirus Antibodies (IgG, IgM) with Reflex to Confirmation

Reference Values:
Reference Range: <2.00

Interpretive Criteria:
<2.00 Antibody not detected
> or = 2.00 Antibody detected

Two major groups of hantaviruses are recognized based on clinical presentation. The first group includes Sin Nombre Virus (SNV), which causes hantavirus pulmonary syndrome, a severe and sometimes fatal form of acute respiratory distress. A second group of hantaviruses (including Seoul, Hantaan, Dobrava, and Puumala) causes hemorrhagic fever with renal syndrome, a condition not typically seen in the United States.

Sera are initially screened for IgG and IgM antibodies recognizing the nucleocapsid protein common to all hantaviruses. All screen IgM positive samples are then tested for SNV-specific IgM; any screen IgM positive samples that are also screen IgG positive are tested for SNV-specific IgG, as well as SNV-specific IgM. Samples that are screen IgG positive but screen IgM negative are not subjected to SNV-specific IgG testing, since the lack of IgM rules out acute SNV infection.

A positive screening result but a negative SNV-specific antibody result may indicate either reactivity to a hantavirus other than SNV or false positive reactivity. A small number of SNV IgM positive (but screen IgG negative) samples represent false positive reactivity associated with acute cytomegalovirus or Epstein Barr virus infection.

HAPT 9168

Haptoglobin, Serum

Clinical Information: Haptoglobin is an immunoglobulin-like plasma protein that binds hemoglobin. The haptoglobin-hemoglobin complex is removed from plasma by macrophages and the hemoglobin is catabolized. When the hemoglobin-binding capacity of haptoglobin is exceeded, hemoglobin passes through the renal glomeruli, resulting in hemoglobinuria. Chronic intravascular hemolysis causes persistently low haptoglobin concentration. Regular strenuous exercise may cause sustained low haptoglobin, presumably from low-grade hemolysis. Low serum haptoglobin may also be due to severe liver disease. Neonatal plasma or serum specimens usually do not contain measurable haptoglobin; adult levels are achieved by 6 months. Increase in plasma haptoglobin concentration occurs as an acute-phase reaction. Levels may appear to be increased in conditions such as burns and nephrotic syndrome. An acute-phase response may be confirmed and monitored by assay of other acute-phase reactants such as
alpha-1-antitrypsin and C-reactive protein.

**Useful For:** Confirmation of intravascular hemolysis

**Interpretation:** Absence of plasma haptoglobin may therefore indicate intravascular hemolysis. However, congenital anhaptoglobinemia is common, particularly in African-Americans. For this reason, it may be difficult or impossible to interpret a single measurement of plasma haptoglobin. If the assay value is low, the test should be repeated after 1 to 2 weeks following an acute episode of hemolysis. If all the plasma haptoglobin is removed following an episode of intravascular hemolysis, and if hemolysis ceases, the haptoglobin concentration should return to normal in a week. Low levels of plasma haptoglobin may indicate intravascular hemolysis.

**Reference Values:**
30-200 mg/dL

**Clinical References:**

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**Hazelnut-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
Hazelnut-Tree, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Interpretation</th>
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<tr>
<td>0</td>
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<td>1</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

HDL-3 cholesterol: 22 - 35 mg/dL

**Heavy Metals Screen Occupational Exposure, Urine**

**Clinical Information:** Arsenic (As), lead (Pb), cadmium (Cd), and mercury (Hg) are well-known toxins and toxic exposures are characterized by increased urinary excretion of these metals. Arsenic exists in a number of different forms; some are toxic while others are not. Toxic forms, which are typically encountered as a result of an industrial exposure, are the inorganic species As (+3) (As-III) and As (+5) (As-V) and the partially detoxified metabolites, monomethylarsine and dimethylarsine. The 2 most common nontoxic forms are arsenobetaine and arsenocholine. Arsenic toxicity affects a number of organ systems. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated renal damage. Mercury is essentially nontoxic in its elemental form. However, once it is chemically modified to the ionized, inorganic species, Hg(++) , it becomes toxic. Further bioconversion to an alkyl mercury, such as methyl Hg (CH[3]Hg[+]), yields a species of mercury that is highly selective for lipid-rich tissue, such as the myelin sheath, and is very toxic.

**Useful For:** Screening potentially exposed workers for heavy metal toxicity in settings where a 24-hour collection is problematic

**Interpretation:** The reference intervals for this test are Occupational Safety and Health Administration (OSHA) thresholds. The ordering physician will be contacted regarding any result exceeding OSHA thresholds to determine the level of workplace exposure and follow-up action. Arsenic results exceeding the OSHA threshold will be fractionated to confirm the presence of toxic forms. Measurement of urine excretion rates either before or after chelation therapy has been used as an indicator of lead exposure. However, blood lead analysis has the strongest correlation with toxicity. Normally, the excretion of cadmium is proportional to creatinine. When renal damage has occurred, cadmium excretion increases relative to creatinine. The correlation between the levels of mercury in the urine and clinical symptoms is poor, but urinary mercury is the most reliable way to assess exposure to inorganic mercury.

**Reference Values:**

- **ARSENIC/CREATININE**
  - <50 mcg/g

- **MERCURY/CREATININE**
  - <35 mcg/g

- **CADMIUM/CREATININE**
  - <3.0 mcg/g

- **LEAD/CREATININE**
  - <5 mcg/g

**Clinical References:** See individual test descriptions for: -ASCRU / Arsenic/Creatinine Ratio, Random, Urine -PBCRU / Lead/Creatinine Ratio, Random, Urine -CDOM / Cadmium Occupational Monitor, Urine -HGOM / Mercury Occupational Monitor, Urine

**Heavy Metals Screen with Demographics, Blood**

**Clinical Information:** Arsenic: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(+5), also denoted as As(V), the more toxic As(+3), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(+3) is oxidized to As(+5) and then methylated to MMA and DMA. As a result of these detoxification steps, As(+3) and As(+5) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because if its affinity for tissue proteins. The body treats arsenic like phosphate,
incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arsenaïsiasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur. Lead: Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of unleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulphydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke. Mercury: Mercury (Hg) is essentially nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(+2), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH[3]Hg(+)), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Not Toxic -- Hg(0) < Hg(+2) << CH(3)Hg(+) -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents such as chlorine. Hg(0) can be bioconverted to both Hg(+2) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(+2), CH(3)Hg(+), and (CH[3])(+2)Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(+2) is readily absorbed and reacts with sulphydryl groups of protein, causing a change in the tertiary structure of the protein-a stereoisomeric change-with subsequent loss of the unique activity associated with that
protein. Because Hg(+2) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as CH(3)Hg(+), are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial flora present in the mouth converts a fraction of this to Hg(+2) and CH(3)Hg(+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain <0.3 mcg/g of mercury, but some game fish contain >2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is <50 mcg/day.

**Useful For:** Detecting exposure to arsenic, lead, cadmium, and mercury

**Interpretation:** Arsenic: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of <6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen. Lead: The 95th percentile of the Gaussian distribution of whole blood lead concentration in a population of unexposed adults is <6.0 mcg/dL. For pediatric patients, there may be an association with blood lead values of 5.0 to 9.9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is >25.0 mcg/dL in children or >45.0 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result >60.0 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels >50.0 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is <40 mcg/dL. New York State has mandated inclusion of the following statement in reports for children under the age of 6 with blood lead in the range of 5.0 to 9.9 mcg/dL: "Blood lead levels in the range of 5.0-9.9 mcg/dL have been associated with adverse health effects in children aged 6 years and younger." Cadmium: Normal blood cadmium is <5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL. Mercury: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually <10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is >50 ng/mL if exposure is due to alkyl Hg, or >200 ng/mL if exposure is due to Hg(+2).

Heavy Metals Screen, 24 Hour, Urine

Clinical Information: See individual test descriptions for:
- ASHMS / Arsenic, 24 Hour, Urine
- CDHMU / Cadmium, 24 Hour, Urine
- PBS / Lead, 24 Hour, Urine
- HGHMS / Mercury, 24 Hour, Urine

Reference Values:

**ARSENIC**
0-35 mcg/specimen
Reference values apply to all ages.

**LEAD**
0-4 mcg/specimen
Reference values apply to all ages.

**CADMIUM**
0-15 years: not established
> or =16 years: 0.0-1.3 mcg/specimen

**MERCURY**
0-15 years: not established
> or =16 years: 0-9 mcg/specimen
Toxic concentration: >50 mcg/specimen
The concentration at which toxicity is expressed is widely variable between patients. 50 mcg/specimen is the lowest concentration at which toxicity is usually apparent.

---

Heavy Metals Screen, Random, Urine

Clinical Information: See individual test descriptions for:
- ASRU / Arsenic, Random Urine
- PBRU / Lead, Random Urine
- CDRU / Cadmium, Random Urine
- HGRU / Mercury, Random Urine

Reference Values:

**ARSENIC**
0-35 mcg/L
Reference values apply to all ages.

**LEAD**
0-4 mcg/L
Reference values apply to all ages.

**CADMIUM**
0-15 years: not established
> or =16 years: 0.0-1.3 mcg/L

**MERCURY**
0-15 years: not established
> or =16 years: 0-9 mcg/L
Toxic concentration: >50 mcg/L
The concentration at which toxicity is expressed is widely variable between patients. 50 mcg/L is the lowest concentration at which toxicity is usually apparent.

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Heavy Metals, Hair

Clinical Information: "See Individual Unit Codes"
Useful For: "See Individual Unit Codes"

Interpretation: "See Individual Unit Codes"

Reference Values:
ARSENIC
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of hair

LEAD
0.0-3.9 mcg/g of hair
Reference values apply to all ages.

MERCURY
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of hair

Clinical References: "See Individual Unit Codes"

Heavy Metals, Nails

Clinical Information: "See Individual Unit Codes"

Useful For: "See Individual Unit Codes"

Interpretation: "See Individual Unit Codes"

Reference Values:
ARSENIC
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of nails

LEAD
0.0-3.9 mcg/g of nails
Reference values apply to all ages.

MERCURY
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of nails

Clinical References: "See Individual Unit Codes"

Helicobacter pylori Antigen, Feces

Clinical Information: Helicobacter pylori is well recognized as the cause of chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia. Currently accepted methods for the diagnosis of Helicobacter pylori infection include, the urea breath test (UBT), and culture or histologic examination or direct urease testing (CLO test) of biopsy specimens obtained at the time of gastroduodenoscopy (ENDO). Each of these tests has its drawbacks, including lack of specificity (serology) or high cost, complexity, and inconvenience for the patient (UBT and ENDO). See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

Useful For: As an aid in the diagnosis of Helicobacter pylori Monitoring the eradication of Helicobacter pylori after therapy (in most situations, confirmation of eradication is not mandatory) The utility of this test in asymptomatic individuals is not known, but testing for Helicobacter pylori in such individuals is not generally recommended

Interpretation: Positive results indicate the presence of Helicobacter pylori antigen in the stool.
Negative results indicate the absence of detectable antigen but does not eliminate the possibility of infection due to Helicobacter pylori.

**Reference Values:**

Negative

**Clinical References:**


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**Helicobacter pylori Breath Test**

**Clinical Information:** The causal relationship between the urease-producing bacterium, Helicobacter pylori, and chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia is well established. Conventional methods for the diagnosis of active Helicobacter pylori infection include evaluation of biopsied gastric tissue by histopathology and culture. Less invasive assays include testing for the presence of Helicobacter pylori antigen in stool specimens and detection of Helicobacter pylori urease production by the Urea Breath Test (UBT). Serologic testing for the presence of IgM/IgG/IgA class antibodies to Helicobacter pylori is also performed; however, this is not recommended by either the American College of Gastroenterologists nor the American Gastroenterological Association (AGA) as an accurate marker for active disease. These serologic markers can remain elevated despite resolution of active disease and may lead to misdiagnosis and/or inappropriate treatment. Recommendations for use of the (13)C-Urea Breath Test (Meretek UBT) were recently provided by the Digestive Health Initiative, a joint committee assembled with representatives from the AGA, the American Society for Gastrointestinal Endoscopy (ASGE), and the American Association for the Study of Liver Diseases (AASLD). These recommendations include the following statements: "When endoscopy is not clinically indicated, the primary diagnosis of Helicobacter pylori infection can be made serologically or with the UBT. When endoscopy is clinically indicated, the primary diagnosis should be established by biopsy urease testing and/or histology. Available evidence suggests that confirmation of Helicobacter pylori eradication is not mandatory in most situations because of costs associated with testing. However, for selected patients with complicated ulcer disease, low-grade gastric mucosa-associated lymphoid tissue lymphoma, and following resection of early gastric cancer, it is appropriate to confirm eradication. In other situations, the decision to confirm Helicobacter pylori eradication should be made on a case-by-case basis." This consensus group further specifies that there is no indication to test asymptomatic people and that testing for Helicobacter pylori is only recommended if treatment is planned. The (13)C-Urea Breath Test (Meretek UBT) is a highly sensitive and specific noninvasive, nonradioactive test for diagnosing Helicobacter pylori infection prior to antimicrobial treatment and for assessing whether the organism has been successfully eradicated following antimicrobial therapy. In 2 recent large prospective studies, the (13)C-UBT was shown to be as, or more, sensitive and specific for diagnosing Helicobacter pylori active infection than culture, PCR, stain, rapid urease testing of biopsy tissue, or serology. When the test is used to assess eradication, it should be performed 4 to 6 weeks after completion of antimicrobial treatment. See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

**Useful For:** Diagnostic testing for Helicobacter pylori infection in patients suspected to have active Helicobacter pylori infection or for monitoring response to therapy

**Interpretation:** The Helicobacter pylori urea breath test can detect very low levels of Helicobacter pylori and, by assessing the entire gastric mucosa, avoids the risk of sampling errors inherent in biopsy-based methods. In the absence of gastric Helicobacter pylori, the (13)C-urea does not produce (13)C02 in the stomach. A negative result does not rule out the possibility of Helicobacter pylori infection. If clinical signs are suggestive of Helicobacter pylori infection, retest with a new specimen or by using an alternative method. A false-positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as Helicobacter heilmannii. A false-positive test could occur in patients who have achlorhydria.

**Reference Values:**

Negative
Helicobacter pylori Culture

**Clinical Information:** Helicobacter pylori is a spiral-shaped gram-negative bacterium that may cause chronic gastritis, peptic ulcer disease, or gastric neoplasia. In adults of industrialized countries, an estimated 0.5% of the susceptible population becomes infected each year, although the incidence has been decreasing over time. The organism may asymptomatically colonize humans. In suspected Helicobacter pylori-associated disease, the noninvasive stool antigen or urea breath test is recommended. If patients fail to respond to treatment and antimicrobial resistance is suspected, a gastric biopsy, gastric brushings, or gastric aspirate may be cultured to attempt to recover the organism for antimicrobial susceptibility testing to assess for resistance.

**Useful For:** Recovery of Helicobacter pylori from gastric specimens for antimicrobial susceptibility testing of the organism

**Interpretation:** A positive result provides definitive evidence of the presence of Helicobacter pylori. Organisms may be detected in asymptomatic (colonized) individuals. False-negative culture results may occur since the organism may die between biopsy collection and laboratory culture.

**Reference Values:**
No growth after 7 days


Helicobacter pylori Culture with Antimicrobial Susceptibilities

**Clinical Information:** Helicobacter pylori is a spiral-shaped gram-negative bacterium that may cause chronic gastritis, peptic ulcer disease, or gastric neoplasia. In adults of industrialized countries, an estimated 0.5% of the susceptible population becomes infected each year, although the incidence has been decreasing over time. The organism may asymptomatically colonize humans. In suspected Helicobacter pylori-associated disease, the noninvasive stool antigen or urea breath test is recommended. If patients fail to respond to treatment and antimicrobial resistance is suspected, gastric biopsy, gastric brushings, or gastric aspirate may be cultured to attempt to recover the organism for antimicrobial susceptibility testing to assess for resistance. Multidrug regimens are required to attain successful cure of Helicobacter pylori infection. Antimicrobial resistance in Helicobacter pylori is increasing. Disease caused by Helicobacter pylori resistant to clarithromycin or metronidazole is associated with a greater incidence of treatment failure than disease caused by a susceptible strain. The Clinical and Laboratory Standards Institute (CLSI) recommends agar dilution for Helicobacter pylori antimicrobial susceptibility testing. Amoxicillin, ciprofloxacin, clarithromycin, metronidazole and tetracycline are routinely tested. The only antimicrobial for which interpretive breakpoints have been defined by the CLSI is clarithromycin.

**Useful For:** Recovery of Helicobacter pylori from gastric specimens for antimicrobial susceptibility testing of the organism (amoxicillin, ciprofloxacin, clarithromycin, metronidazole and tetracycline are routinely tested)

**Interpretation:** A positive result provides definitive evidence of the presence of Helicobacter pylori. Organisms may be detected in asymptomatic (colonized) individuals. False-negative culture results may occur since the organism may die between biopsy collection and laboratory culture. When antimicrobial susceptibilities are performed, definitions of susceptible, susceptible-dose dependent, intermediate, resistant, and nonsusceptible are as follows: Susceptible (S) The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used. Susceptible-Dose Dependent (D) The "susceptible-dose dependent" category implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for
which the susceptibility testing results are in the D category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved dosage regimen, because higher exposure gives the highest probability of adequate coverage of a D isolate. The drug label should be consulted for recommended doses and adjustment for organ function. The D category may be assigned when doses well above those used to calculate the susceptible breakpoint are approved and used clinically. Intermediate (I) The "intermediate" category includes isolates with antimicrobial agent minimum inhibitory concentrations (MIC) that approach usually attainable blood and tissue levels, and for which response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins. Resistant (R) The "resistant" category implies that the isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies. Nonsusceptible (N) The "nonsusceptible" category is used for isolates for which only a susceptible interpretive criterion has been designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above the value indicated for the susceptible breakpoint is reported as nonsusceptible. Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

**Reference Values:**
No growth after 7 days
Susceptibility results are reported as MIC in mcg/mL

**Clinical References:** Theel ES. Helicobacter pylori Infection: Test Utilization Strategies for Diagnosis. Mayo Medical Laboratories Communique 2013;38(6):1-8

**Helminthosporium halodes, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
<table>
<thead>
<tr>
<th>Class</th>
<th>Comment</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Below Detection</td>
<td>&lt;0.35 kU/L</td>
</tr>
<tr>
<td>1</td>
<td>Low Positive</td>
<td>0.35 – 0.69</td>
</tr>
<tr>
<td>2</td>
<td>Moderate Positive</td>
<td>0.70 – 3.49</td>
</tr>
<tr>
<td>3</td>
<td>Positive</td>
<td>3.50 – 17.49</td>
</tr>
<tr>
<td>4</td>
<td>Strong Positive</td>
<td>17.50 – 49.99</td>
</tr>
<tr>
<td>5</td>
<td>Very Strong Positive</td>
<td>50.00 – 99.99</td>
</tr>
<tr>
<td>6</td>
<td>Very Strong Positive</td>
<td>&gt;99.99</td>
</tr>
</tbody>
</table>


**FHSSE 57532**

**Helminthosporium sativum/Drechslera IgE**

**Interpretation:** Class IgG (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**HOLDC 35848**

**Hematologic Disorders, Chromosome Hold, Bone Marrow or Peripheral Blood**

**Clinical Information:** Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, chromosome analysis may not be necessary. Depending on the diagnosis, FISH assays may also be more informative.

**Useful For:** Holding the bone marrow or peripheral blood specimen in the laboratory but delaying chromosome analysis while preliminary morphologic assessment is in process

**Interpretation:** If notified by the client, this test may be canceled and a processing fee assessed. If no notification to cancel testing is received, this test will be reported as "reflexed for chromosome analysis" and depending on the specimen received, CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow or CHRHB / Chromosome Analysis, Hematologic Disorders, Blood will be performed and an interpretive report provided.

**Reference Values:**

Not applicable

**EXHB 60562**

**Hematologic Disorders, DNA/RNA Extract and Hold, Blood**

**Clinical Information:** It is frequently useful to obtain nucleic acid from clinical samples containing a hematopoietic neoplasm at the time of diagnosis, so that appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually...
no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acid on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

**Useful For:** Reserving nucleic acid on any specimen for which molecular analysis may be necessary at a future date, ensuring that adequate material for testing is available

**Interpretation:** A report of "Performed" will be sent and a $75 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

**Reference Values:**
Not applicable

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**Hematologic Disorders, DNA/RNA Extract and Hold, Bone Marrow**

**Clinical Information:** It is frequently useful to obtain nucleic acid from clinical specimens containing a hematopoietic neoplasm at the time of diagnosis, so that appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acid on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

**Useful For:** Reserving nucleic acid on any specimen for which molecular analysis may be necessary at a future date, ensuring that adequate material for testing is available

**Interpretation:** A report of "Performed" will be sent and a $75 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

**Reference Values:**
Not applicable

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**Hematologic Disorders, Fluorescence In Situ Hybridization (FISH) Hold, Bone Marrow or Peripheral Blood**

**Clinical Information:** Fluorescence in situ hybridization (FISH) analysis using gene-specific probes is a useful methodology to detect common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, FISH analysis may not be necessary. Depending on the diagnosis, conventional chromosome analysis may also be more informative.

**Useful For:** Processing the bone marrow or peripheral blood specimen but delaying FISH analysis while preliminary morphologic assessment is in process

**Interpretation:** If notified by the client, this test may be canceled and a processing fee will be assessed. If no notification to cancel testing is received, this test will be reported as "reflexed for FISH analysis," and the FISH assay indicated in the test order will be performed and an interpretive report provided.

**Reference Values:**
Not applicable
Hematologic Disorders, Leukemia/Lymphoma; Flow Hold Varies

Clinical Information: Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

Useful For: Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

Interpretation: Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

Reference Values: When performed, an interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist.


Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9

Clinical Information: Patients with chronic lymphocytic leukemia (CLL) have variable disease course influenced by a series of tumor biologic factors. The presence of chromosomal 17p- or TP53 gene mutation confers a very poor prognosis to a subset of CLL patients, both at time of initial diagnosis, as well as at disease progression, or in the setting of therapeutic resistance. TP53 gene mutation status in CLL has emerged as the single most predictive tumor genetic abnormality associated with adverse outcome and poor response to standard immunochemotherapy; however, patients can be managed with alternative therapeutic options. Although the prognostic relevance of acquired TP53 gene mutation is best studied for CLL, similar findings are also reported for other hematologic malignancies including low grade B-cell lymphoma, diffuse large B-cell lymphoma, and some types of myelodysplastic syndromes.
(MDS) and acute myeloid leukemia (AML). Therefore, while this test has been developed to be primarily focused on high risk CLL patients, p53 gene sequencing analysis can also be performed in additional neoplasms, as clinically indicated. This test is NOT intended for the evaluation of patients suspected of having an inherited, or germ line TP53 mutation cancer syndrome (eg, Li Fraumeni syndrome); if this is intended as a clinical indication, see TP53Z / TP53 Gene, Full Gene Analysis.

**Useful For:** Evaluating chronic lymphocytic leukemia patients at diagnosis or during disease course for the presence of TP53 gene mutations indicating high risk of disease progression and adverse outcome

This test is complementary to FISH analysis for the 17p- abnormality, but more appropriately identifies the presence of mutational alteration and gene inactivation in tumor cells. For hereditary (germ line) TP53 mutation syndrome testing, see TP53Z / TP53 Gene, Full Gene Analysis.

**Interpretation:** The presence of TP53 gene mutations indicate high risk of disease progression and adverse outcome.

**Reference Values:**

Mutation(s) present or absent as compared to a reference sequence of the normal TP53 gene

**Clinical References:**


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**Hematopathology Consultation, Wet Tissue**

**Clinical Information:** Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. The clinical, therapeutic, and prognostic features of these disorders are often distinctive, while the pathologic features are quite subtle, requiring the application of ancillary studies (eg, cytochemistry, immunohistochemistry, flow cytometric immunophenotyping, cytogenetics, and molecular genetics) to establish a diagnosis. Furthermore, these ancillary studies are expensive, labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. It is the Division of Hematopathology's goal to provide the highest possible level of diagnostic consultative service, trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems. All blood and bone marrow studies are available within the context of a hematopathology consultation. If requesting a full bone marrow workup, the Mayo consultant will approach the diagnosis in a way consistent with Mayo Clinic practice. The Mayo Hematopathologist may call the referring physician/pathologist to discuss the case prior to performing any additional studies. Referring physicians are welcome to suggest which specific ancillary studies should be performed, but before they are done, a morphologic review by one of the Mayo consulting staff hematopathologists will confirm the diagnostic problem presented by the morphologic differential diagnosis.

**Useful For:** Obtaining a rapid, expert opinion on unprocessed specimens referred by the primary pathologist Obtaining special studies not available locally

**Interpretation:** Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is
completed, results may be communicated by a phone call. The formal pathology report is faxed. In our consultative practice, we strive to bring the customer the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

Reference Values:
The laboratory will provide a pathology consultation.

**FHME**  
**Hemiplegic Migraine Evaluation**

Reference Values:  
A final report will be attached in MayoAccess.

**HFE**  
**Hemochromatosis HFE Gene Analysis, Blood**

**Clinical Information:** Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism with a carrier frequency of approximately 1 in 10 individuals of northern European ancestry. The disease is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues. Iron overload can cause hepatic cirrhosis, hepatocellular carcinoma, diabetes mellitus, arthropathy, and cardiomyopathy. Such complications can generally be prevented by phlebotomy, and patients have a normal life expectancy if treated before organ damage occurs. For individuals with clinical symptoms consistent with HH or biochemical evidence of iron overload, an HH diagnosis is typically based on the results of transferrin-iron saturation and serum ferritin concentration. Molecular testing can be done to confirm the diagnosis. The majority of HH patients have mutations in the HFE gene. Clinically significant iron overload also can occur in the absence of known HFE mutations, so a negative HFE test does not exclude a diagnosis of iron overload or hemochromatosis. The most common mutation in the HFE gene is C282Y (exon 4, 845G->A). Homozygosity for the C282Y mutation is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of individuals affected with HH are heterozygous for this mutation. These frequencies show variability among different populations, with the highest frequency observed in individuals of northern European ancestry. Penetration for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical end points (such as diabetes mellitus, hepatic cirrhosis, and cardiomyopathy) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms. The H63D (exon 2, 187C->G) mutation is associated with HH, but the actual clinical effects of this mutation are uncertain. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of additional modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations. Approximately 1% to 2% of individuals with this genotype will develop clinical evidence of iron overload. While individuals with this genotype may have increased iron indices, most will not develop clinical disease without comorbid factors (steatosis, diabetes, or excess alcohol consumption). The clinical significance of a third HFE mutation, S65C (exon 2, 193A->T), appears to be minimal. This rare variant displays a very low penetrance. Compound heterozygosity for C282Y and S65C may confer a low risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type or H63D alleles do not seem to be at an increased risk for HH. The S65C mutation is only reported when it is part of the C282Y/S65C genotype. Refer to What's New in Hereditary Hemochromatosis, Mayo Medical Laboratories Communiqué 2005 April;30(4) for more information regarding diagnostic strategy. See Hereditary Hemochromatosis Algorithm in Special Instructions.

**Useful For:** Establishing or confirming the clinical diagnosis of hereditary hemochromatosis (HH) in adults HFE genetic testing is NOT recommended for population screening Testing of individuals with increased transferrin-iron saturation in serum and serum ferritin With appropriate genetic counseling, predictive testing of individuals who have a family history of HH

**Interpretation:** An interpretive report will be provided. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

Reference Values:
An interpretative report will be provided.

**Clinical References:**

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**Hemoglobin A1c, Blood**

**Clinical Information:** Diabetes mellitus is a chronic disorder associated with disturbances in carbohydrate, fat, and protein metabolism characterized by hyperglycemia. It is one of the most prevalent diseases, affecting approximately 24 million individuals in the United States. Long-term treatment of the disease emphasizes control of blood glucose levels to prevent the acute complications of ketosis and hyperglycemia. In addition, long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease can be minimized if blood glucose levels are effectively controlled. Hemoglobin A1c (HbA1c) is a result of the nonenzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The attachment of the hexose molecule occurs continually over the entire life span of the erythrocyte and is dependent on blood glucose concentration and the duration of exposure of the erythrocyte to blood glucose. Therefore, the HbA1c level reflects the mean glucose concentration over the previous period (approximately 8-12 weeks, depending on the individual) and provides a much better indication of long-term glycemic control than blood and urinary glucose determinations. Diabetic patients with very high blood concentrations of glucose have from 2 to 3 times more HbA1c than normal individuals. Diagnosis of diabetes includes 1 of the following: -Fasting plasma glucose ≥ 126 mg/dL -Symptoms of hyperglycemia and casual plasma glucose ≥ 200 mg/dL -Two-hour glucose ≥ 200 mg/dL during oral glucose tolerance test unless there is unequivocal hyperglycemia, confirmatory testing should be repeated on a different day In addition, recommendations from the American Diabetes Association (ADA) include the use of HbA1c to diagnose diabetes, using a cutpoint of 6.5%. The cutpoint was based upon sensitivity and specificity data from several studies. Advantages to using HbA1c for diagnosis include: -HbA1c provides an assessment of chronic hyperglycemia -Assay standardization efforts from the National Glycohemoglobin Standardization Program have been largely successful and the accuracy of HbA1c is closely monitored by manufacturers and laboratories -No fasting is necessary -Intraindividual variability is very low (critical value of <2%) -A single test could be used for both diagnosing and monitoring diabetes When using HbA1c to diagnose diabetes, an elevated HbA1c should be confirmed with a repeat measurement, except in those individuals who are symptomatic and also have an increased plasma glucose >200 mg/dL. Patients who have an HbA1c between 5.7 and 6.4 are considered at an increased risk for developing diabetes in the future. (The terms prediabetes, impaired fasting glucose, and impaired glucose tolerance will eventually be phased out by the ADA to eliminate confusion.) The ADA recommends measurement of HbA1c (typically 3-4 times per year for type 1 and poorly controlled type 2 diabetic patients, and 2 times per year for well-controlled type 2 diabetic patients) to determine whether a patient's metabolic control has remained continuously within the target range.

**Useful For:** Evaluating the long-term control of blood glucose concentrations in diabetic patients Diagnosing diabetes Identifying patients at increased risk for diabetes (prediabetes)

**Interpretation:** Diagnosing diabetes American Diabetes Association (ADA) -Hemoglobin A1c (HbA1c) > 6.5% Therapeutic goals for glycemic control (ADA) -Adults: - Goal of therapy: <7.0% HbA1c - Action suggested: >8.0% HbA1c -Pediatric patients: - Toddlers and preschoolers: <8.5% (but >7.5%) - School age (6-12 years): <8% - Adolescents and young adults (13-19 years): <7.5% The 2009 ADA recommendations for clinical practice suggest maintaining a HbA1c value closer to normal yields improved microvascular outcomes for diabetics. Target goals of <7% may be beneficial in patients such as those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. However, in patients with significant complications of diabetes, limited life expectancy, or...
extensive comorbid conditions, targeting a <7% goal may not be appropriate. Since the HbA1c assay reflects long-term fluctuations in blood glucose concentration, a diabetic patient who has in recent weeks come under good control may still have a high concentration of HbA1c. The converse is true for a diabetic previously under good control who is now poorly controlled. HbA1c results <4.0% are reported with the comment: "Falsey low HbA1c results may be observed in patients with clinical conditions that shorten erythrocyte life span or decrease mean erythrocyte age. HbA1c may not accurately reflect glycemic control when clinical conditions that affect erythrocyte survival are present. Fructosamine may be used as an alternate measurement of glycemic control."

Reference Values:
> or =18 years: 4.0-6.0%

Reference values have not been established for patients who are <18 years of age.

Clinical References:

Hemoglobin A2 and F, Blood

Clinical Information: Hemoglobin F (Hb F), composed of 2 alpha and 2 gamma globin chains, is the normal hemoglobin of the fetus and newborn. Normally in the second trimester, gamma chain production (and Hgb F levels) decrease and beta chain production increases, resulting in increasing levels of hemoglobin A (Hb A), the major normal adult hemoglobin (2 alpha and 2 beta globin chains). Hemoglobin A2 (Hb A2) (2 alpha and 2 delta globin chains) also comprises a small amount (<3.3%) of hemoglobin normally found in adults. Hb A2 values at birth are <1%.

Useful For: Assisting in the diagnosis of beta-thalassemia Quantitating the percent of hemoglobin F (Hb F) present Assisting in the diagnosis of disorders with elevated levels of Hb F

Interpretation: Hemoglobin A2 (Hb A2) values of 3.5% to 9% are found in beta-thalassemia trait. In beta-thalassemia major, hemoglobin F (Hb F) may be 30% to 90% or even more of the total hemoglobin. Hb F concentration is usually between 5% to 15% of the total hemoglobin in delta/beta-type thalassemia trait (F-thalassemia). Higher concentrations of Hg F occur in hemoglobin S (Hb S)/beta zero-thalassemia, in patients who are doubly heterozygous for the Hgb S gene, and in patients who have a gene for hereditary persistence of fetal hemoglobin (HPFH). These disorders may be differentiated by family studies or by flow cytometry studies for Hgb F (HPFH / Hemoglobin F, Red Cell Distribution, Blood), which reveals uniform intraerythrocytic distribution of Hgb F in HPFH and nonuniform distribution in Hgb S/beta thalassemia. The electrophoretic finding of small quantities of Hb A in a patient who has mostly Hgb S and a moderate increase in Hb F is strong evidence of Hgb S/beta thalassemia (if the patient has not had a transfusion). Hb F values greater than normal (2%) may be seen in chronic anemias, beta-thalassemia, and HPFH

Reference Values:
HEMOGLOBIN A2
1-30 days: 0.0-2.1%
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%
> or =6 months: 2.0-3.3%

HEMOGLOBIN F
1-30 days: 22.8-92.0%
1-2 months: 7.6-89.8%
3-5 months: 1.6-42.2%
6-8 months: 0.0-16.7%
9-12 months: 0.0-10.5%
13-17 months: 0.0-7.9%
18-23 months: 0.0-6.3%
> or =24 months: 0.0-0.9%


Hemoglobin Electrophoresis Cascade, Blood

Clinical Information: A large number (>800) of variants of hemoglobin (Hb) have been recognized. They are identified by capital letters (eg, Hb A or Hb S), or by the city in which the variant was first discovered (eg, Hb Koln). Mayo Medical Laboratories receives specimens for this test from a wide geographic area and nearly one-half of all specimens received exhibit abnormalities. The most common abnormality is an increase in Hb A2 to about 4% to 8%, which is diagnostic of beta-thalassemia minor. A wide variety of other hemoglobinopathies also have been encountered. Ranked in order of relative frequency, these are: Hb S (sickle cell disease and trait), C, E, Lepore, G-Philadelphia, H, D-Los Angeles, Koln, Constant Spring, O-Arab, and others. Hb C and S are found mostly in people from west or central Africa and Hb E and H in people from Southeast Asia. Hemoglobin electrophoresis is often used in the evaluation of unexplained microcytosis, thus accounting for the frequent detection of Hb Lepore, which is relatively common in Italians and others of Mediterranean ancestry and in Hb E, which is relatively common in Southeast Asians resettled in the United States; microcytosis is characteristic of both Hb Lepore and Hb E. Alpha-thalassemia is very common in the United States, occurring in approximately 30% of African Americans and accounting for the frequent occurrence of microcytosis in persons of this ethnic group. Some alpha-thalassemias (ie, hemoglobin variants H, Barts, and Constant Spring) are usually easily identified in the hemoglobin electrophoresis protocol. However, alpha-thalassemias that are from only 1 or 2 alpha-globin gene deletions are not recognized. Unfortunately, there is no easy test for the diagnosis of these alpha-thalassemias (see ATHAL / Alpha-Globin Gene Analysis). Alpha-thalassemia trait itself is a harmless condition.

Useful For: Diagnosis of thalassemias and hemoglobin variants Evaluation of unexplained microcytosis

Interpretation: The types of hemoglobin present are identified, quantitated, and an interpretive report is issued.

Reference Values:

HEMOGLOBIN A
1-30 days: 5.9-77.2%
1-2 months: 7.9-92.4%
3-5 months: 54.7-97.1%
6-8 months: 80.0-98.0%
9-12 months: 86.2-98.0%
13-17 months: 88.8-98.0%
18-23 months: 90.4-98.0%
> or =24 months: 95.8-98.0%

HEMOGLOBIN A2
1-30 days: 0.0-2.1%
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%
> or =6 months: 2.0-3.3%

HEMOGLOBIN F
1-30 days: 22.8-92.0%
Hemoglobin F, Blood

Clinical Information: Fetal hemoglobin concentration is usually between 5% to 15% of the total hemoglobin in the high F or delta/beta-type of thalassemia minor. In beta-thalassemia major, fetal hemoglobin may be 30% to 90% or even more of the total hemoglobin. Slight increases in hemoglobin F concentration are found in a variety of unrelated hematologic disorders, such as aplastic anemia, hereditary spherocytosis, and myeloproliferative disorders. In homozygous sickle cell disease, hemoglobin F concentration is often slightly increased. Higher concentrations of hemoglobin F occur in hemoglobin S/beta O-thalassemia, in patients who are doubly heterozygous for the hemoglobin S gene, and in patients who have a gene for hereditary persistence of fetal hemoglobin (HPFH). These disorders may be differentiated by family studies or by flow cytometry studies for fetal hemoglobin, which reveals uniform intraerythrocytic distribution of hemoglobin F in HPFH and nonuniform distribution in hemoglobin S/beta-thalassemia. The electrophoretic finding of small quantities of hemoglobin A in a patient who has mostly hemoglobin S and a moderate increase in hemoglobin F is strong evidence of hemoglobin S/beta zero thalassemia (if the patient has not had a transfusion).

Useful For: Quantitating the percent of fetal hemoglobin present Assisting in the diagnosis of disorders with elevated levels of fetal hemoglobin

Interpretation: See Clinical Information and Reference Values.

Reference Values:
- 1-30 days: 22.8-92.0%
- 1-2 months: 7.6-89.8%
- 3-5 months: 1.6-42.2%
- 6-8 months: 0.0-16.7%
- 9-12 months: 0.0-10.5%
- 13-17 months: 0.0-7.9%
- 18-23 months: 0.0-6.3%
- > or =24 months: 0.0-0.9%

**Hemoglobin F, Red Cell Distribution, Blood**

**Clinical Information:** More than 75% of the hemoglobin of the newborn is hemoglobin F (Hb F); it diminishes over a period of several months to adult levels, becoming <2% by 1 year-of-age and <1% by 2 years. Hb F may constitute 90% of the total hemoglobin in patients with beta-thalassemia major or other combinations of beta thalassemia and fetal hemoglobin (HPFH) mutations. Hb F is often mildly to moderately elevated in sickle cell disease, aplastic anemia, acute leukemia, myeloproliferative disorders such as juvenile myelomonocytic leukemia (JMML), hereditary spherocytosis, and alpha-thalassemia minor. It is commonly increased in hemoglobinopathies associated with hemolysis. Hb F increases to as high as 10% during normal pregnancy. Hb F is also increased due to medications such as hydroxyurea, decitabine, and lenalidomide. Elevation in Hb F has a been cited as a discriminator between Diamond-Blackfan congenital pure red cell aplasia (elevated) and transient erythroblastopenia of childhood (normal) but whether this simply reflects the chronicity of anemia inherent to the former condition rather than a specific finding is unclear. In the common (large deletional) form of the genetic trait hereditary persistence of HPFH, all of the erythrocytes contain Hb F. When tested by flow cytometry using specificity for Hb F, these HPFH cases display a homocellular distribution pattern of Hb F within the red cell population. Other causes of increased Hb F including delta beta thalassemia, hydroxyurea, and some nondeletional HPFH mutations typically display a heterocellular distribution of Hb F within the red cells, reflecting disparate populations of F cells and cells lacking Hb F. Quantification of Hb F percentage should be determined prior to flow cytometry of Hb F red cell distribution to establish the appropriateness of this test. The flow cytometry analysis of elevated Hb F levels is useful when Hb F percentage is between 15% to 35% and the clinical differential diagnosis includes large deletional HPFH. Hb F percentages below 15% are likely not due to large deletional HPFH and causes of Hb F percentages above 35% are better confirmed by molecular and family studies. This test is not to be ordered for fetal-maternal bleed. If fetal maternal bleed assessment is desired, please see FMB / Fetomaternal Bleed, Flow Cytometry, Blood.

**Useful For:** Distinguishing large deletional hereditary persistence of fetal hemoglobin from other conditions with increased percentage of fetal hemoglobin

**Interpretation:** Homocellular distribution of fetal hemoglobin is found in large deletional hereditary persistence of fetal hemoglobin. Heterocellular distribution is found in delta beta thalassemia, medication induced, and other causes of increased hemoglobin F.

**Reference Values:** Reported as heterocellular or homocellular

**Clinical References:**

**Hemoglobin S and Hemoglobin F Quantitation for Therapeutic Monitoring, Blood**

**Clinical Information:** The treatment of red blood cell sickling disorders may involve many therapeutic modalities. Two of the most important and beneficial are treatment with hydroxyurea and chronic transfusion therapy. Hydroxyurea causes elevation of hemoglobin F (Hb F) levels, and transfusion serves to lower the percentage of hemoglobin S (Hb S). Both of these therapeutic modalities act to lessen the number and severity of sickling crises. Thus, periodic monitoring of Hb F and Hb S levels are needed to guide further therapy.
**Useful For:** Monitoring patients with sickling disorders who have received hydroxyurea or transfusion therapy

**Interpretation:** Optimal levels of hemoglobin S and hemoglobin F are patient specific and depend on a number of factors including response to therapy.

**Reference Values:**

**HEMOGLOBIN F**
- 1-30 days: 22.8-92.0%
- 1-2 months: 7.6-89.8%
- 3-5 months: 1.6-42.2%
- 6-8 months: 0.0-16.7%
- 9-12 months: 0.0-10.5%
- 13-17 months: 0.0-7.9%
- 18-23 months: 0.0-6.3%
- > or =24 months: 0.0-0.9%

**HEMOGLOBIN S**
- All ages: 0.0%

**Clinical References:**

**SDEX**

**Hemoglobin S, Screen, Blood**

**Clinical Information:** Homozygous hemoglobin S (sickle cell disease) is a serious chronic hemolytic anemia most commonly found in those of African or Middle Eastern descent. Hemoglobin S is freely soluble when fully oxygenated; when oxygen is removed, polymerization of the abnormal hemoglobin occurs, forming tactoids that are rigid and deformed cells. This leads to sickling of the cells, hemolysis, and many other complications. Heterozygous hemoglobin S (sickle cell trait) is the most common hemoglobinopathy in the United States. This condition is present in about 8% of African Americans. Usually, hemoglobin S trait exhibits no clinical or hematological effects. A small fraction of people with sickle cell trait have recurrent hematuria.

**Useful For:** Screening for hemoglobin S (sickle cell trait)

**Interpretation:** A positive result should be followed by hemoglobin electrophoresis to confirm the presence and concentration of hemoglobin S.

**Reference Values:**

- Negative

**Precautions:** The procedure does not distinguish hemoglobin S trait from homozygous sickle cell disease nor any of the following combinations: S/C, S/D, S/G, S/E, S/thalassemia, S/O-Arab, S/New York and C-Georgetown trait (Hb C-Harlem).


**HGB_Q**

**Hemoglobin, Qualitative, Urine**

Current as of July 8, 2016 11:28 am CDT   800-533-1710 or 507-266-5700 or MayoMedicalLabs.com   Page 955
**Clinical Information:** Free hemoglobin (Hgb) in urine usually is the result of lysis of RBCs present in the urine due to bleeding into the urinary tract (kidney, ureters, bladder). Less commonly, intravascular hemolysis (e.g., transfusion reaction, hemolytic anemia, paroxysmal hemoglobinuria) may result in excretion of free Hgb from blood into urine. Injury to skeletal or cardiac muscle results in the release of myoglobin, which also is detected by this assay. Conditions associated with myoglobinuria include hereditary myoglobinuria, phosphorylase deficiency, sporadic myoglobinuria, exertional myoglobinuria in untrained individuals, crush syndrome, myocardial infarction, myoglobinuria of progressive muscle disease, and heat injury.

**Useful For:** Screening for hematuria, myoglobinuria, or intravascular hemolysis

**Interpretation:** Free hemoglobin (Hgb), in the presence of RBCs, indicates bleeding into the urinary tract. Free Hgb, in the absence of RBCs, is consistent with intravascular hemolysis. Note: RBCs may be missed if lysis occurred prior to analysis; the absence of RBCs should be confirmed by examining a fresh specimen. The test is equally sensitive to hemoglobin and to myoglobin. The presence of myoglobin may be confirmed by MYOU / Myoglobin, Urine.

**Reference Values:**
Appearance (internal specimens only): normal
Hemoglobin: negative
RBCs (internal specimens only): 0-2 rbcs/hpf

**Clinical References:** Fairbanks, V.F. and Klee G.G., Textbook of Clinical Chemistry 1986, Chapter 15, p 1562

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**HAEVP 84157 Hemolytic Anemia Evaluation**

**Clinical Information:** Hemolytic anemia (HA) is characterized by increased red cell destruction and a decreased red cell life span. Patients usually have decreased hemoglobin concentration, hematocrit, and red blood cell count, but some can have compensated disorders, and symptoms such as reticulocytosis, pigmented gallstones, and decreased haptoglobin are factors that raise clinical suspicion. Blood smear abnormalities may include spherocytes, schistocytes, stomatocytes, polychromasia, basophilic stippling, and target cells. Osmotic fragility can be increased due to the presence of spherocytes. HAs may be congenital or acquired. Inherited hemolytic disorders may include red cell membrane disorders, red cell enzyme defects, or abnormalities in the hemoglobin molecule in the red cell. This panel assesses for possible causes of congenital/hereditary causes of hemolytic anemia and does not evaluate for acquired causes. Therefore, the anemia should be lifelong or familial in nature. Examples of acquired HA, which should be excluded prior to ordering this panel, include: autoimmune HA, direct Coombs-positive HA, cold agglutinin disease, disseminated intravascular coagulation, and drug-induced HA. This consultative evaluation looks for the cause of increased red cell destruction and includes testing for red cell membrane disorders, such as hereditary spherocytosis, hemoglobinopathies, and red cell enzyme abnormalities.

**Useful For:** Evaluation of lifelong or inherited hemolytic anemias

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Definitive results and an interpretive report will be provided.


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**F8INP 66206 Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling**
Clinical Information: Hemophilia A (HA) is due to a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 and 22 inversion mutations account for approximately 50% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: Prenatal testing for hemophilia A when a mutation has not been identified in the family.

Interpretation: An interpretive report will be provided.

Reference Values: Not applicable

Clinical References:
Inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** First-tier molecular testing for males affected with severe hemophilia A when a mutation has not been identified in the family. Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A

**Interpretation:** An interpretive report will be provided.

**Reference Values:** Not applicable

**Clinical References:**

**F81P**

**Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling**

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding is the most common clinical symptom in individuals with HA and correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion mutation accounts for approximately 5% of mutations associated with severe HA. This inversion is typically not identified in patients with mild or moderate HA. Intron 1 inversion known mutation analysis on a prenatal specimen can only be performed when there is a known intron 1 inversion in the family. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** Prenatal testing for hemophilia A when a F8 intron 1 inversion has been identified in a family member.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** Not applicable
Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation, Whole Blood

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion mutation accounts for approximately 5% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 1 inversion known mutation analysis is only recommended for individuals when an intron 1 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 1 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: First-tier molecular testing for males affected with severe hemophilia A, when a familial intron 1 inversion has been previously identified. Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A due to F8 intron 1 inversion

Interpretation: An interpretive report will be provided.

Reference Values: Not applicable

Whole Blood

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion mutations account for approximately 45% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known mutation analysis is only recommended for individuals when an intron 22 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 22 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** First-tier molecular testing for males affected with severe hemophilia A, when a familial intron 22 inversion has been previously identified. Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A due to F8 intron 22 inversion

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Not applicable

**Clinical References:**

F822P 89454

**Hemophilia A F8 Gene, Intron 22 Inversion Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling**

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA,
bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion mutations account for approximately 45% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intronic inversion mutation analysis on a prenatal specimen can only be performed when there is a known intron 22 inversion in the family. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** Prenatal testing for hemophilia A when a F8 intron 22 inversion has been identified in a family member.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Not applicable

**Clinical References:**

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**Hemophilia B, F9 Gene Known Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling**

**Clinical Information:** Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves, and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of hemophilia B patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX:antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

**Useful For:** Prenatal testing for a known familial pathogenic mutation in the F9 gene in a fetus who is at risk for inheriting this mutation

**Interpretation:** An interpretive report will be provided.
**Reference Values:**
An interpretive report will be issued that will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation).

**Clinical References:**

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**FIXKM 84320**

**Hemophilia B, F9 Gene Known Mutation, Whole Blood**

**Clinical Information:** Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves, and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

**Useful For:** Diagnostic, targeted testing for hemophilia B when a mutation has been identified in a family member Carrier testing of females in whom the familial F9 genotype is known

**Interpretation:** An interpretive report will be provided.

**Reference Values:** Not applicable

**Clinical References:**

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**F9MAP 64576**

**Hemophilia B, F9 Gene Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling**

**Clinical Information:** Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX...
activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX:antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

**Useful For:** Prenatal testing for a pathogenic mutation in the F9 gene in a fetus with a strong, confirmed family history of congenital hemophilia B (factor IX activity deficiency) in the exceptional circumstance where a familial mutation cannot be otherwise ascertained

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be issued that will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation and carrier status).

**Clinical References:**

**Hemophilia B, F9 Gene Mutation Analysis, Whole Blood**

**Clinical Information:** Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males. However, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of hemophilia patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

**Useful For:** Ascertainment of the causative mutation in the F9 gene of patients with congenital hemophilia B (factor IX activity deficiency) Carrier testing of females in whom the familial F9 genotype is unknown

**Interpretation:** An interpretive report will be issued which will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation and carrier status).

**Reference Values:**
Not applicable

**Clinical References:**
1. Yoshitake S, Schach BG, Foster DC, et al: Nucleotide sequence of the gene

HemoQuant, Feces

Clinical Information: Several noninvasive tests are available to detect gastrointestinal (GI) bleeding. However, guaiac type and immunochemical tests for occult bleeding are affected by the presence of reducing or oxidizing substances and are insensitive for the detection of proximal gut bleeding, where most clinically significant occult GI bleeding occurs. The HemoQuant test is the most reliable, noninvasive test currently available for detecting bleeding of the esophago-GI tract. Unlike other tests for blood in feces, this test detects both intact heme and porphyrins from partly degraded heme. Additionally, test results are not complicated by either the water content of the specimen or the presence of reducing or oxidizing substances. Furthermore, HemoQuant testing is sensitive to both proximal and distal sources of occult GI bleeding.

Useful For: Detection of blood in feces HemoQuant is the most appropriate fecal occult blood test to use in the evaluation of iron deficiency Other useful applications include the detection of bleeding as a complication of anticoagulant therapy and other medication regimens

Interpretation: Elevated levels are an indicator of the presence of blood in the feces, either from benign or malignant causes. This test is not specific for bowel cancer.

Reference Values:
Normal:
< or =2.0 mg total hemoglobin/g feces
Marginal:
2.0-3.0 mg total hemoglobin/g feces
2.0-4.0 mg total hemoglobin/g feces*
Elevated:
>3.0 mg total hemoglobin/g feces
>4.0 mg total hemoglobin/g feces*
*Alternative reference values for persons who have ingested red meat or aspirin during any of the 3 days preceding specimen collection.


Hemosiderin, Urine

Clinical Information: When the plasma hemoglobin level is >50 to 200 mg/dL after hemolysis, the capacity of haptoglobin to bind hemoglobin is exceeded, and hemoglobin readily passes through the glomeruli of the kidney. Part of the hemoglobin is absorbed by the proximal tubular cells where the hemoglobin iron is converted to hemosiderin. When these tubular cells are later shed into the urine, hemosiderinuria results. If all of the hemoglobin cannot be absorbed into the tubular cells, hemoglobinuria results. Hemosiderin is found as yellow-brown granules that are free or in epithelial cells and occasionally in casts in an acidic or neutral urine.

Useful For: Detecting hemosiderinuria, secondary to excess hemolysis, as in incompatible blood transfusions, severe acute hemolytic anemia, or hemochromatosis
Interpretation: A positive hemosiderin indicates excess red cell destruction. Hemosiderinuria may still be detected after hemoglobin has cleared from the urine and hemoglobin dipstick is negative.

Reference Values:
- Hemosiderin: negative (reported as positive or negative)
- Hemoglobin (internal specimens only): negative
- RBC (internal specimens only): 0-2 rbc/hpf


**Hemp Western Water (Acnida tamariscina) IgE**

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

**Heparin Anti-Xa Assay, Plasma**

Clinical Information: Heparins are sulphated glycosaminoglycans that inactivate thrombin, factor Xa, and several other coagulation factors; act by enhancing activity of the plasma coagulation inhibitor, antithrombin III (AT III); prolong the activated partial thromboplastin time (APTT); of low molecular weight heparin have minimal effect on the APTT, and require an alternative method, such as the anti-Xa assay, to monitor therapy.

Useful For: Measuring heparin concentration - In patients treated with low molecular weight heparin preparations - In presence of prolonged baseline activated partial thromboplastin time (APTT) (eg, lupus anticoagulant, "contact factor" deficiency, etc.) - When unfractionated heparin dose needed to achieve desired APTT prolongation is unexpectedly higher (>50%) than expected

Interpretation: Therapeutic ranges: Adults > or =18 years - Standard heparin (UFH): 0.30 to 0.70 IU/mL - Low molecular weight heparin (LMWH): 0.50 to 1.00 IU/mL for twice daily dosing (specimen drawn 4-6 hours following subcutaneous injection) or 1.00 to 2.00 IU/mL for once daily dosing (specimen drawn 4-6 hours following subcutaneous injection) Children <8 weeks - Standard heparin (UFH): 0.30 to 0.70 IU/mL - LMWH: 0.50 to 1.00 IU/mL (specimen drawn 4-6 hours following subcutaneous injection) - LMWH (prophylactic): 0.10 to 0.30 IU/mL

Reference Values:
- > or =18 years
  - UFH therapeutic range: 0.30-0.70 IU/mL
  - LMWH therapeutic range: 0.50-1.00 IU/mL for twice daily dosing
    - 1.00-2.00 IU/mL for once daily dosing (sample obtained 4-6 hours following subcutaneous injection)

- > or =8 weeks-17 years
  - UFH therapeutic range: 0.30-0.70 IU/mL
  - LMWH therapeutic range: 0.50-1.00 IU/mL (sample obtained 4-6 hours following subcutaneous injection)

- <8 weeks
  - LMWH prophylactic range: 0.10-0.30 IU/mL

Reference values have not been established for patients who are less than 8 weeks of age.

Clinical References: 1. Marci CD, Prager D: A review of the clinical indications for the plasma

**FHPCF**

**Heparin Cofactor II**

**Reference Values:**

65 - 145%

**HIT**

**Heparin-PF4 Antibody (HIT), Serum**

**Clinical Information:** Thrombocytopenia in patients treated with heparin is relatively common and has diverse, sometimes multifactorial, causes. Among the possible causes of thrombocytopenia in such patients, immune-mediated heparin-dependent thrombocytopenia (HIT) is clinically important because of its frequency and its associated risk of paradoxical new or progressive thrombosis. HIT, also called heparin-associated thrombocytopenia (HAT), consists of 2 distinct clinicopathologic syndromes. The first, sometimes designated type I HIT (HIT-I) or nonimmune HAT, is a common benign condition that is not immunologically mediated. Type I HIT is characterized by a mild decrease of the platelet count (typically ≤30% decrease from baseline) occurring early (days) in the course of treatment with heparin, especially intravenous unfractionated heparin (UFH), and which does not progress and may resolve despite continuation of heparin therapy. The second, more serious immune-mediated syndrome, sometimes designated type II heparin-induced thrombocytopenia (HIT-II), occurs in up to 1% to 5% of patients treated with UFH. It is typically characterized by onset of thrombocytopenia between days 5 and 10 of UFH therapy, but thrombocytopenia can arise earlier or later in association with continued heparin exposure. In patients recently exposed to heparin (eg, within the preceding 3-6 months), onset of thrombocytopenia can be rapid (within 24 hours) after heparin reexposure, probably reflecting persistence of heparin-dependent antplatelet antibodies or anamnestic recall of them. Typically, during the course of HIT-II, the platelet count decreases by at least 40% to 50% from baseline or the postoperative peak (in surgical patients), even though the absolute count may remain normal, and thrombocytopenia resolves within 7 to 14 days of cessation of heparin therapy (unless there is another coexisting cause of thrombocytopenia). The risk of immune-mediated HIT-II is significantly greater with UFH exposure than with exposure to low molecular weight heparin (LMWH), although the latter can react with heparin-dependent antibodies induced by UFH. The risk is probably also associated with the dosage and route of heparin administration (eg, intravenous), as well as associated medical and surgical conditions. HIT-II is clinically important, not because of the mild or moderate thrombocytopenia and minimal bleeding risk, but because of the high risk for development of paradoxical thrombosis (arterial or venous) that may be new or progressive. This evolution, termed heparin-induced thrombocytopenia with thrombosis (HITT) syndrome, can occur in up to 30% to 50% of patients with HIT-II, even following discontinuation of heparin therapy. Clinically, it is often difficult to distinguish between HIT-I and HIT-II and among other etiologies of thrombocytopenia occurring in patients receiving heparin. However, the development of new or progressive thrombosis is one defining clinical feature of HIT-II. Recent studies provide evidence that HIT-II is caused, in at least 90% of cases, by antibodies to antigen complexes of heparinoid (heparin or similar glycosaminoglycans) and platelet factor 4 (PF4). PF4 is a platelet-specific heparin-binding (neutralizing) protein that is abundant in platelet alpha granules from which it is secreted following platelet stimulation. A reservoir of PF4 normally accumulates upon vascular endothelium. Following heparin administration, immunogenic complexes of PF4 and heparin can provide an antigenic stimulus for antibody development in some patients. Antibodies bound to platelets that display complexes of PF4/heparin antigen can activate platelets via interaction of the Fc immunoglobulin tail of the IgG.
antibody with platelet Fc gamma IIA receptors, leading to perpetuation of the pathologic process that can cause platelet-rich thrombi in the microcirculation in some cases (eg, HITT syndrome). Functional assays for HIT-II antibody detection rely on antibody-mediated heparin-dependent platelet activation, as detected by platelet aggregation, or platelet secretion of serotonin or adenosine triphosphate (ATP) or other substances, using patient serum or plasma supplemented with heparin and normal test platelets from carefully selected donors. The sensitivity of functional assays for HIT-II ranges from 50% to 60% for heparin-dependent platelet aggregation (HDPA) assays, to 70% to 80% for serotonin release assays. The specificity of positive functional tests for HIT diagnosis is believed to be high (> or =90%). However, because of their complexity, functional tests for detecting HIT antibodies are not widely available. Enzyme-linked immunosorbent assays (ELISAs) have recently been developed to detect HIT-II antibodies and are based on the detection of human antibodies that react with solid phase antigen complexes of heparinoid and human PF4 (H/PF4 complexes). The ELISA for H/PF4 antibodies is very sensitive for antibody detection, but relatively nonspecific for clinical HIT diagnosis. Routine screening of all patients prior to, during, or following heparin use is currently not recommended. A positive H/PF4 ELISA result has relatively low and uncertain predictive value for the development of clinical HIT-II.

**Useful For:** Evaluation of possible immune-mediated type II heparin-induced thrombocytopenia (HIT-II) which should be suspected for the following patients:  
- Patients not previously exposed to heparin, the development of absolute thrombocytopenia or decrease in platelet count of > or =50% from baseline or postoperative peak with the onset of thrombocytopenia beginning approximately 5 to 10 days after initiation of heparin. This may or may not be associated with new or progressive thrombosis in patients treated with heparin.  
- Patients previously exposed to heparin (especially within the preceding 100 days), in addition to the above findings, the onset of thrombocytopenia could occur within 24 to 48 hours after reexposure to heparin. In patients with prior suspected or documented heparin-induced thrombocytopenia (HIT), with or without thrombosis, assay for presence of human platelet factor 4 (H/PF4) antibody may be useful in assessment of the risk of recurrence of HIT with additional exposure to heparin, however, prospective data are limited.

**Interpretation:** Results are reported as: 1) Reactivity (%); 2) Heparin inhibition (%); 3) Interpretation. Typical patterns of results and interpretations are depicted in the following table. Interpretive comments will also accompany test reports, when indicated. Reactivity (%) Heparin Inhibition (%) Interpretation  
Normal Range <20 Not done Negative  
Positive  
Equivocal  
>40 >50 >40 >50 >40 >50 >50 Equivocal  
A negative result of testing for human platelet factor 4 (H/PF4) antibodies has about a 90% negative predictive value for exclusion of clinical type II heparin-induced thrombocytopenia (HIT-II). Because up to 10% of patients with clinical heparin-induced thrombocytopenia (HIT) may have a negative H/PF4 antibody enzyme-linked immunosorbent assay (ELISA) result, a negative H/PF4 antibody ELISA result does not exclude the diagnosis of HIT when clinical suspicion remains high. A functional assay for HIT antibodies (eg, heparin-dependent platelet aggregation or serotonin release assay may be helpful in these circumstances). Contact Mayo Medical Laboratories for ordering information. A positive result is indicative of the presence of H/PF4 complex antibodies. However, this test's specificity is as low as 20% to 50% for clinical diagnosis of HIT, depending on the patient population studied. For example, up to 50% of surgical patients and up to 20% of medical patients treated with heparin may develop H/PF4 antibodies as measured by ELISA, and only a small proportion (1%-5%) develop clinical HIT. Accordingly, this test does not confirm the diagnosis of HIT-II. The diagnosis must be made in conjunction with clinical findings, including evaluation for other potential causes of thrombocytopenia. The presence of H/PF4 antibodies likely increases the risk of clinical HIT, with risk probably partly dependent on associated medical and surgical conditions, but currently there are few data about relative risk of HIT in various populations with positive tests for H/PF4 antibodies.

**Reference Values:**

<20%

**Clinical References:**  
HAVM 8342

Hepatitis A IgM Antibody, Serum

Clinical Information: Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted primarily by the fecal-oral route, and it is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral routes (eg, exposure to blood) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. Serological diagnosis of acute viral hepatitis A depends on the detection of specific anti-HAV IgM. Its presence in the patient's serum indicates a recent exposure to HAV. Anti-HAV IgM becomes detectable in the blood within 2 weeks after infection, persisting at elevated levels for about 2 months before declining to undetectable levels by 6 months. However, sensitive immunoassays may occasionally detect anti-HAV IgM for up to 1 year after acute hepatitis A.

Useful For: Diagnosis of acute or recent hepatitis A infection

Interpretation: A positive result indicates acute or recent (<6 months) hepatitis A infection. As required by laws in almost all states, positive antihepatitis A virus (anti-HAV) IgM test results must be urgently reported to state health departments for epidemiologic investigations of possible outbreak transmission. A negative result may indicate either 1) inadequate or delayed HAV IgM response after known exposure to HAV, or 2) absence of acute or recent hepatitis A. Borderline anti-HAV IgM test results may be seen in: 1) early acute hepatitis A associated with rising antibody levels, 2) recent hepatitis A associated with declining levels, or 3) cross-reactivity with nonspecific antibodies (ie, false-positive results). Retesting of both anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) and anti-HAV total (HAV / Hepatitis A Total Antibodies, Serum) in 2 to 4 weeks is recommended to determine the definitive HAV infection status.

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.


FHASQ 75120

Hepatitis A Qualitative PCR HAV SuperQual

Clinical Information: The direct detection of HAV is a valuable tool in determining whether a patient undergoing therapeutic treatment has cleared the virus. It is also useful in determining whether blood or blood products are free of detectable HAV prior to distribution to patients. PCR is able to directly detect HAV RNA and does not rely on later markers such as antigens and antibodies that are not produced in newly infected individuals.

Useful For: Detect and quantify Hepatitis A Virus DNA (HAV DNA).

Interpretation: The presence of target-specific nucleic acid is indicative of infection. Mean Detection: 24.98 copies/mL (12.81 IU/mL) 95% Detection Cutoff: 61.83 copies/mL (31.71 IU/mL)

Reference Values:
Negative

HAV 83330

Hepatitis A Total Antibodies, Serum

Clinical Information: Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted
primarily by the fecal-oral route, and it is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral routes (eg, exposure to blood) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. In most cases, antibodies to HAV (anti-HAV) are detectable by the time that symptoms occur, usually 15 to 45 days after exposure. Initial antibodies consist almost entirely of the IgM subclass. Anti-HAV IgM usually falls to an undetectable level by 6 months after HAV infection. Anti-HAV IgG levels rise quickly once the virus is cleared and may persist for many years. Currently, commercial diagnostic assays are available for detecting only anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) or anti-HAV total (IgM and IgG), but not anti-HAV IgG alone.

**Useful For:** Detection of recent or previous exposure or immunity to hepatitis A

**Interpretation:** This assay detects the presence of anti-HAV total (both IgG and IgM combined). A positive result indicates that the patient had hepatitis A either recently or in the past or immunity to hepatitis A from vaccination. If clinically indicated, specific testing for anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) is necessary to confirm the presence of acute or recent hepatitis A. A positive result for anti-HAV total (HAV / Hepatitis A Total Antibodies, Serum) with a negative anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) result indicates immunity to hepatitis A from either past HAV infection or vaccination against HAV. A negative result indicates the absence of recent or past hepatitis A or a lack of immunity to HAV infection. Borderline test results for anti-HAV total may be seen in: 1) acute hepatitis A with rising levels of anti-HAV IgM, 2) recent hepatitis with rising levels of anti-HAV IgG, or 3) cross-reactivity with nonspecific antibodies (ie, false-positive results). Retesting of both anti-HAV total (HAV / Hepatitis A Total Antibodies, Serum) and anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) is recommended to determine the definitive HAV infection status.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**
acute, recent, past/resolved exposure to hepatitis A, or immunity to hepatitis A from vaccination. Testing for anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) is necessary to confirm the presence of acute or recent hepatitis A. A positive anti-HAV total result with a negative anti-HAV IgM result indicates immunity to hepatitis A from either past/resolved hepatitis A or vaccination against hepatitis A. Negative results indicate the absence of recent or past hepatitis A or a lack of immunity to HAV infection. Borderline test results for anti-HAV total may be seen in: 1) acute hepatitis A with rising levels of anti-HAV IgM, 2) recent hepatitis with rising levels of anti-HAV IgG, or 3) cross-reactivity with nonspecific antibodies (ie, false-positive results). Retesting of both anti-HAV total and anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) is recommended to determine the definitive HAV infection status.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

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**HBIM 9015**

**Hepatitis B Core Antibody, IgM, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. In the initial (acute) phase of infection, anti-hepatitis B core antibodies (anti-HBc) consist almost entirely of the IgM antibody class and appear shortly after the onset of symptoms. Anti-HBc IgM antibody can be detected in serum and is usually present for up to 6 months after acute HBV infection. Anti-HBc IgM may be the only serologic marker of a recent hepatitis B infection detectable following the disappearance of hepatitis B surface antigen (HBsAg) and prior to the appearance of hepatitis B surface antibody (anti-HBs) (ie, serologic window period). See Viral Hepatitis Serologic Profile in Special Instructions and The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications.

**Useful For:** Diagnosis of acute hepatitis B infection Identifying acute hepatitis B virus (HBV) infection in the serologic window period when hepatitis B surface antigen and anti-hepatitis B surface are negative Differentiation between acute and chronic/past hepatitis B infection in the presence of positive anti-hepatitis B core

**Interpretation:** A positive result indicates recent acute hepatitis B infection. A negative result suggests lack of recent exposure to the virus in preceding 6 months.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

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**HBC 8347**

**Hepatitis B Core Total Antibodies, Serum**

**Clinical Information:** Hepatitis B core antibodies (anti-HBc Ab) appear shortly after the onset of symptoms of hepatitis B infection and soon after the appearance of hepatitis B surface antigen (HBsAg). Initially, anti-HBc Ab consist almost entirely of the IgM class, followed by appearance of anti-HBc IgG, for which there is no commercial diagnostic assay. The anti-HBc total antibodies test, which detects both IgM and IgG antibodies, and the test for anti-HBc IgM antibodies may be the only markers of a recent hepatitis B infection detectable in the "window period." The window period begins with the clearance of HBsAg and ends with the appearance of antibodies to hepatitis B surface antigen (anti-HBs Ab). Anti-HBc total Ab may be the only serologic marker remaining years after exposure to hepatitis B.

**Useful For:** Diagnosis of recent or past hepatitis B infection Determination of occult hepatitis B
infection in otherwise healthy hepatitis B virus (HBV) carriers with negative test results for hepatitis B surface antigen, antihepatitis B surface, antihepatitis B core IgM, hepatitis Be antigen, and anti-HBe. This assay is not useful for differentiating among acute, chronic, and past/resolved hepatitis B infection. This assay is FDA-approved for in vitro diagnostic use and not for screening cell, tissue, and blood donors.

**Interpretation:** A positive result indicates acute, chronic, or past/resolved hepatitis B.

**Reference Values:**

<table>
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<td>Interpretation depends on clinical setting.</td>
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See Viral Hepatitis Serologic Profiles in Special Instructions.


**CORAB 32111** Hepatitis B Core Total Antibodies, with Reflex to Hepatitis B Core Antibody, IgM, Serum

**Clinical Information:** During the course of a typical case of acute hepatitis B viral (HBV) infection, IgM antibodies to hepatitis B core antigen (anti-HBc IgM) are present in the serum shortly before clinical symptoms appear. Anti-HBc total is detectable during the prodromal, acute, and early convalescent phases when it exists as immunoglobulin M (IgM) anti-HBc. Anti-HBc IgM rises in level and is present during the core window period, ie, after hepatitis B surface antigen disappears and before antibodies to hepatitis B surface antigen appear. Anti-HBc total may be the only serologic marker remaining years after exposure to HBV.

**Useful For:** Detection and differentiation between recent and past/resolved or chronic hepatitis B viral (HBV) infection Diagnosis of recent HBV infection during the "window period" when both hepatitis B surface antigen and antibodies to hepatitis B surface antigen are negative

**Interpretation:** A positive, antibodies to hepatitis B core antigen (anti-HBc) total result may indicate, either, recent, past/resolved, or chronic hepatitis B viral (HBV) infection. Testing for anti-HBc IgM (HBIM / Hepatitis B Core Antibody, IgM, Serum) is necessary to confirm the presence of acute or recent hepatitis B. A positive anti-HBc total result with a negative anti-HBc IgM result indicates past or chronic HBV infection. Differentiation between past/resolved and chronic hepatitis B can be based on the presence of hepatitis B surface antigen in the latter condition. Negative anti-HBc total results indicate the absence of recent, past/resolved, or chronic hepatitis B.

**Reference Values:**

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<td>Interpretation depends on clinical setting.</td>
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See Viral Hepatitis Serologic Profiles in Special Instructions.


**HBABY 63137** Hepatitis B Perinatal Exposure Follow-up Panel, Serum

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic; others may develop chronic liver disease including cirrhosis and hepatocellular carcinoma. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen (HBsAg) carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the
first or second trimester of pregnancy. Without post-exposure prophylaxis (a combination of HBV vaccination and hepatitis B immune globulin), the risk of an infant acquiring HBV from an infected mother as a result of perinatal exposure is 70% to 90% for infants born to mothers who are positive for HBsAg and HBeAg. The risk is 5% to 20% for infants born to HBsAg-positive but HBeAg-negative mothers. HBV is also spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles by drug addicts). The virus is found in virtually every type of human body fluid and also is spread through oral and genital contact.

**Useful For:** Determining hepatitis B virus infection and immunity status in infants born to mothers with chronic hepatitis B and after receiving perinatal prophylaxis

**Interpretation:** Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in blood at 6 to 16 weeks after exposure to HBV. A confirmed positive HBsAg result is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for >6-month duration indicates development of either a chronic carrier state or chronic hepatitis B. Hepatitis B surface (HBs) antibody appears with the resolution of HBV infection and disappearance of HBsAg. A positive result indicates recovery from acute or chronic hepatitis B, or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and recovery from HBV infection. Positive results (HBs Ab levels of >10.0 mIU/mL) indicate adequate immunity to hepatitis B. After receiving a primary HBV vaccine series, individuals with HBs Ab levels of > or =10 mIU/mL are considered protected from hepatitis B in accordance with the CDC guideline (CDC. Immunization of health-care personnel. MMWR 2011;60[No. SS-7]:5). A negative result (HBs levels of <10.0 mIU/mL) indicates a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. Hepatitis B core (HBc) total antibodies (combined IgG and IgM) appear shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to HBV. A positive result indicates exposure to HBV infection. A positive HBs antibody result along with a positive HBc total antibody result is indicative of recovery from HBV infection. A positive HBs antibody result with a negative HBc total antibody result is consistent with immunity to hepatitis B from HBV vaccination. See Viral Hepatitis Serologic Profiles in Special Instructions.

**Reference Values:**

Negative

**Clinical References:**

HBV markers and the clinical presentation and history of the patient. Before the onset of clinical illness, HBsAg is detectable in the serum and its presence persists through the symptomatic phase of illness. Following clinical illness, the titer of HBsAg begins to decline and eventually falls below a detectable level. After HBsAg disappears, hepatitis B surface antibody (anti-HBs) appears in the serum, although there is often a gap called the "window period" between the disappearance of HBsAg and the appearance of anti-HBs. In approximately 10% of patients, HBsAg persists indefinitely in the serum, indicating a chronic carrier state, and anti-HBs does not appear. During the course of a typical case of acute hepatitis B infection, hepatitis B core antibody (anti-HBc) is present in the serum shortly before clinical symptoms appear. It is detectable during prodromal, acute, and early convalescent phases where it exists as immunoglobulin M (IgM) anti-HBc. Total anti-HBc (IgG and IgM) rises in titer and is present during the "window period," ie, after HBsAg disappears and before anti-HBs appears. For this reason, in the absence of other HBV markers, total anti-HBc is considered a reliable indicator of ongoing infection. It is also an accurate serological marker of previous HBV infection, as it appears in all patients infected with the HBV and may persist in individuals at low titer (as IgG anti-HBc) long after HBV exposure. Although total anti-HBc is a long-lived antibody, in some cases total anti-HBc titers, along with total anti-HBs, may fall into the undetectable range. In subclinical asymptomatic HBV infection, HBsAg and hepatitis Be antigen (HBeAg) are present for a brief period or may not be detectable and are followed by the appearance of anti-HBc and anti-HBs. In these patients, detection of total anti-HBc and total anti-HBs must be relied on as evidence of previous HBV infection. In chronic HBV, HBsAg appears during the incubation phase of the disease and may persist for years and possibly for life. Total anti-HBc also appears during this early phase and rises in titer. The highest titers of total anti-HBc are found in the chronic HBsAg carrier state. Total anti-HBc may be negative or undetectable in serum or plasma during the early acute phase of HBV infection and long after infection resolution, when titers may fall. The presence of anti-HBs in serum indicates previous exposure to HBV and acquired immunity. Low titers of anti-HBs in serum, however, can signal a lack of immunity to future HBV infection. The clinical relevance of anti-HBs detection is in establishing complete resolution of the infection and the acquisition of immunity, whether acquired as a result of natural HBV infection or vaccination. Anti-HBs may fall below detectable levels with time. See Viral Hepatitis Serologic Profiles in Special Instructions.

**Reference Values:**

**HEPATITIS B SURFACE ANTIGEN**

Negative

**HEPATITIS B CORE TOTAL ANTIBODY**

Negative

**HEPATITIS B SURFACE ANTIBODY**

Unvaccinated: negative  
Vaccinated: positive

**HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE**

Unvaccinated: <5.0 mIU/mL  
Vaccinated: > or =12.0 mIU/mL

Interpretation depends on clinical setting.  
See Viral Hepatitis Serologic Profiles in Special Instructions.


**HBA BT 87893**

**Hepatitis B Surface Antibody Monitor, Post-Transplant, Serum**

**Clinical Information:** For patients with chronic hepatitis B virus (HBV) infection (hepatitis B surface antigen-positive), outcomes following liver transplantation for end-stage liver disease are poor. Recurrent HBV disease is common and associated with decreased liver graft and patient survival (approximately
Studies have shown administration of hepatitis B immune globulin (HBIG) in the perioperative and early posttransplant periods could delay or prevent recurrent HBV infection in these transplant recipients. Intravenous or intramuscular administration of HBIG has become the standard of care for these liver transplant recipients in most liver transplant programs in the United States since mid-1990. Most therapy protocols administer HBIG in high doses (10,000 IU) during the perioperative period and first week after transplantation, with the goal of achieving serum hepatitis B surface antibody (anti-HBs) levels of >500 mIU/mL. Serial levels of anti-HBs are obtained to determine the pharmacokinetics of HBIG in each patient to guide frequency of HBIG dosing. There is a high degree of variability in HBIG dosage required to achieve desirable serum anti-HBs levels among transplant recipients during the first few weeks to months after transplantation. Patients who were hepatitis B envelope (HBe) antigen positive before transplantation usually require more HBIG to achieve the target anti-HBs levels, especially in the first week after transplantation. Duration of HBIG therapy varies from 6 months to indefinite among different US liver transplant programs. Protocols providing <12 months of therapy usually combine HBIG with another effective anti-HBV agent such as lamivudine. See HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

**Useful For:** Monitoring serum anti-hepatitis B surface levels during intravenous or intramuscular hepatitis B immune globulin therapy to prevent hepatitis B virus reinfection in liver transplant recipients with known previous chronic hepatitis B

**Interpretation:** Please refer to health care provider's institutional hepatitis B immune globulin (HBIG) therapy protocol for desirable hepatitis B surface antibody (anti-HBs) levels. Studies indicated that serum anti-HBs levels needed to prevent hepatitis B virus reinfection were >500 mIU/mL during the first week after transplantation, >250 mIU/mL during weeks 2 to 12, and >100 mIU/mL after week 12. See HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

**Reference Values:**
Not applicable

**Clinical References:**

**Clinical Information:** Hepatitis B virus (HBV) infection, also known as serum hepatitis, is endemic throughout the world. The infection is spread primarily through blood transfusion or percutaneous contact with infected blood products, such as sharing of needles among injection drug users. The virus is also found in virtually every type of human body fluid and has been known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but is not commonly transmitted via the transplacental route. The incubation period for HBV infection averages 60 to 90 days (range of 45-180 days). Common symptoms include malaise, fever, gastroenteritis, and jaundice (icterus). After acute infection, HBV infection becomes chronic in 30% to 90% of infected children <5 years of age and in 5% to 10% of infected individuals >5 years of age. Some of these chronic carriers are asymptomatic, while others progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) is the first serologic marker, appearing in the serum 6 to 16 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms with the appearance of hepatitis B surface antibody (anti-HBs). Anti-HBs also appears as the immune response following hepatitis B vaccination. See The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications and HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions.

**Useful For:** Identifying previous exposure to hepatitis B virus Determining adequate immunity from hepatitis B vaccination

**Interpretation:** This assay provides both qualitative and quantitative results. A positive result indicates recovery from acute or chronic hepatitis B virus (HBV) infection, or acquired immunity from HBV
vaccination. This assay does not differentiate between a vaccine-induced immune response and an immune response induced by infection with HBV. A positive total anti-hepatitis B core (anti-HBc) result would indicate that the hepatitis B surface antibody (anti-HBs) response is due to past HBV infection. Positive results (quantitative hepatitis B surface antibody [anti-HBs] levels of > or =12.0 mIU/mL) indicate adequate immunity to hepatitis B from past hepatitis B or HBV vaccination. After receiving a primary HBV vaccine series, individuals with anti-HBs levels of 12 mIU/mL or greater are considered protected from hepatitis B in accordance with the CDC guideline.(1) A negative result (quantitative anti-HBs level of <5.0 mIU/mL) indicates a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. The U.S. Advisory Committee on Immunization Practices does not recommend more than 2 HBV vaccine series in nonresponders.(1) Indeterminate results (quantitative anti-HBs levels in the range from > or =5 to <12 mIU/mL) indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 3 months. See The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications and HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions.

Reference Values:
HEPATITIS B SURFACE ANTIBODY
Unvaccinated: negative
Vaccinated: positive

HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE
Unvaccinated: <5.0 mIU/mL
Vaccinated: > or =12.0 mIU/mL

See Viral Hepatitis Serologic Profiles in Special Instructions.


Hepatitis B Surface Antigen Confirmation Prenatal, Serum
Clinical Information: Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for >6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. See The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile

Useful For: Diagnosis of acute, recent, or chronic hepatitis B infection in prenatal patients

Interpretation: A reactive screen result confirmed as positive by hepatitis B surface antigen (HBsAg) confirming test is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with reactive screen results but negative (ie, not confirmed) HBsAg confirming test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. Repeat testing is recommended at a later date if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B envelope (HBe) antigen and/or detectable HBV DNA. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV
Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile

**Reference Values:**
Only orderable as a reflex. For more information see HBAGP / Hepatitis B Surface Antigen Prenatal, Serum

**Clinical References:**

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**HBAGP**

**Hepatitis B Surface Antigen Prenatal, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy.

**Useful For:** Stand-alone prenatal screening test for chronic hepatitis B in pregnant women

**Interpretation:** A reactive screen result confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with initially reactive test results, but negative (not confirmed) by HBsAg confirmation test, are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg-reactive screening test results should be interpreted in conjunction with test results of other HBV serologic markers (e.g., hepatitis B surface antibody; hepatitis B core antibody, total and IgM). The presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by the presence of hepatitis B envelope (HBe) antigen and/or detectable HBV DNA.

**Reference Values:**
Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

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**HBAG**

**Hepatitis B Surface Antigen, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for >6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. See The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile

**Useful For:** Diagnosis of acute, recent, or chronic hepatitis B infection Determination of chronic
Interpretation: A reactive screen result (signal to cutoff ratio [S/CO] > or =1.00, but < or =50.0) confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test (see Method Description) or a positive screen result (S/CO >50.0) is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with reactive screen results but negative (ie, not confirmed) HBsAg confirmatory test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. Repeat testing is recommended at a later date if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B envelope (HBe) antigen and/or detectable HBV DNA. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

Clinical References:

Hepatitis B Virus (HBV) DNA Detection and Quantification by Real-Time PCR, Serum

Clinical Information: Diagnosis of acute or chronic hepatitis B virus (HBV) infection is based on the presence of HBV serologic markers such as hepatitis B surface antigen (HBsAg) and hepatitis B core IgM antibody (anti-HBc IgM), or the presence of HBV DNA detected by molecular assays. Although the diagnosis of acute and chronic HBV infection is usually made by serologic methods, detection and quantification of HBV DNA in serum are useful to: -Diagnose some cases of early acute HBV infection (before the appearance of HBsAg) -Distinguish active from inactive HBV infection -Monitor a patient's response to anti-HBV therapy The presence of HBV DNA in serum is a reliable marker of active HBV replication. HBV DNA levels are detectable by 30 days following infection, generally reach a peak at the time of acute hepatitis, and gradually decrease and disappear when the infection resolves spontaneously. In cases of acute viral hepatitis with equivocal HBsAg test results, testing for HBV DNA in serum may be a useful adjunct in the diagnosis of acute HBV infection, since HBV DNA can be detected approximately 21 days before HBsAg typically appears in the serum. Patients with chronic HBV infection fail to clear the virus and remain HBsAg-positive. Such cases may be further classified as chronic active (replicative) HBV (high HBV levels, hepatitis Be antigen [HBeAg]-positive) or chronic inactive (nonreplicative) HBV (low or undetectable HBV DNA levels, HBeAg-negative). HBV DNA levels in serum are useful in determining the status of chronic HBV infection, by differentiating between active and inactive disease states. Patients with chronic active HBV are at greater risk for more serious liver disease and are more infectious than patients with inactive HBV infection. Reactivation of inactive chronic HBV infection (HBeAg-negative state) may occur with or without reappearance of HBeAg in serum. In patients with HBeAg-negative disease, detection of HBV DNA is the only reliable marker of active HBV replication. The therapeutic goal of anti-HBV therapy in patients who are HBeAg-positive is to achieve long-term suppression of viral replication with undetectable HBV DNA, HBe seroconversion and loss of HBeAg. The therapeutic goal in patients with HBeAg-negative disease is typically long-term viral suppression. The emergence of drug-resistant HBV strains (in response to treatment with nucleos(t)ide analogs, eg, lamivudine, adefovir, entecavir, tenofovir), is characterized by either the reappearance of HBV DNA in serum (after it had become undetectable) or an increase in HBV DNA levels (following an initial decline). See HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions and HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

Useful For: Confirmation of chronic hepatitis B virus (HBV) infection Quantification of HBV DNA in serum of patients with chronic HBV infection (previously hepatitis B surface antigen-positive) Monitoring disease progression in chronic HBV infection and/or response to anti-HBV therapy

Interpretation: The quantification range of this assay is 20 to 170,000,000 IU/mL (1.30-8.23 log

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
IU/mL). An "Undetected" result indicates that hepatitis B virus (HBV) DNA was not detected in the specimen. A "Detected" result with the comment, "HBV DNA level is <20 IU/mL (<1.30 log IU/mL). This assay cannot accurately quantify HBV DNA below this level" indicates that the HBV DNA level is below the lower limit of quantification for this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HBV viral replication in the patient. Monitoring HBV DNA levels over time is important for assessing disease progression or monitoring a patient's response to anti-HBV therapy. A "Detected" result with the comment, "HBV DNA level is >170,000,000 IU/mL (>8.23 log IU/mL). This assay cannot accurately quantify HBV DNA above this level" indicates that the HBV DNA level is above the upper limit of quantification for this assay. An indeterminate result with the comment "Inconclusive Result: Submit a new specimen for testing if clinically indicated" indicates that inhibitory substances may be present in the specimen. When clinically indicated, collection and testing of a new specimen is recommended.

**Reference Values:**

**Undetected**

**Clinical References:**
1. Pawlotsky JM: Hepatitis B virus (HBV) DNA assays (methods and practical use) and viral kinetics. J Hepatol 2003;39:S31-S35

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**Hepatitis B Virus Genotyping**

**FHBG 57618**

**Reference Values:**

**Interpretive Information: Hepatitis B Virus Genotype**

HBV genotype and resistance interpretation is provided by SeqHepB software from Evivar Medical. The following mutations are reported: reverse transcriptase L80I/V, I69T, V173L, L180M, A181S/T/V, T184A/C/F/I/G/S/M/L, S202C/G/I, M204I/V, N236T, M250I/L/V; surface antigen P120T, D144A, G145R.

Both the HBV RT polymerase and the HBsAg encoding regions are sequenced. Resistance and surface antigen mutations are reported. In addition, the major HBV genotypes are identified. Mutations in viral sub-populations below 20% of total may not be detected.

This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.

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**Hepatitis Be Antibody, Serum**

**HEAB 80973**

**Clinical Information:** During recovery from acute hepatitis B, the hepatitis Be antigen level declines and becomes undetectable and hepatitis Be antibody (anti-HBe) appears in the serum. Anti-HBe usually remains detectable for several years after recovery from acute infection. In hepatitis B virus (HBV) carriers and in patients with chronic hepatitis B, positive anti-HBe results usually indicate inactivity of the virus and low infectivity of the patients. Positive anti-HBe results in the presence of detectable HBV DNA in serum indicate active viral replication. See HBV Infection-Diagnostic Approach and Management Algorithm and Viral Hepatitis Serologic Profile in Special Instructions. Also see The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications.

**Useful For:** Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of chronically HBV-infected patients Monitoring serologic response of chronically HBV-infected patients who are receiving antiviral therapy
**Interpretation:** Absence of hepatitis Be (HBe) antigen with appearance of HBe antibody is consistent with loss of hepatitis (HBV) infectivity. Although resolution of chronic HBV infection generally follows appearance of HBe antibody, the HBV carrier state may persist.

**Reference Values:**

Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.


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**HEAG**

**Hepatitis Be Antigen and Hepatitis Be Antibody, Serum**

**Clinical Information:** Hepatitis Be antigen (HBeAg) is found in the early phase of hepatitis B infection soon after hepatitis Bs antigen becomes detectable. Serum levels of both antigens rise rapidly during the period of viral replication. The presence of HBeAg correlates with hepatitis B virus (HBV) infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and presence of viral DNA polymerase in serum. During recovery from acute hepatitis B, after HBeAg level declines and becomes undetectable, HBe antibody (anti-HBe) appears in the serum. Anti-HBe usually remains detectable for several years after recovery from acute infection. In HBV carriers and chronic hepatitis B patients, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or lack of HBV replication. Positive anti-HBe results usually indicate inactivity of the virus and low infectivity. Positive anti-HBe results in the presence of detectable HBV DNA in serum indicate active viral replication in these patients.

**Useful For:** Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of chronically HBV-infected patients Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy

**Interpretation:** Presence of hepatitis Be (HBe) antigen and absence of HBe antibody usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBe antigen with appearance of HBe antibody is consistent with loss of HBV infectivity. Although resolution of chronic HBV infection generally follows appearance of HBe antibody, the HBV carrier state may persist.

**Reference Values:**

**HEPATITIS BE ANTIGEN**

Negative

**HEPATITIS BE ANTIBODY**

Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.


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**EAG**

**Hepatitis Be Antigen, Serum**

**Clinical Information:** Hepatitis Be antigen (HBeAg) is found in the early phase of hepatitis B infection soon after hepatitis Bs antigen becomes detectable. Serum levels of both antigens rise rapidly during the period of viral replication. The presence of HBeAg correlates with hepatitis B virus (HBV) infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and presence of viral DNA polymerase in serum. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or lack of HBV replication. See Viral
Hepatitis Serologic Profile and HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions. In addition, see The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications.

**Useful For:** Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of chronically HBV-infected patients Monitoring serologic response of chronically HBV-infected patients who are receiving antiviral therapy

**Interpretation:** Presence of hepatitis Be (HBe) antigen and absence of HBe antibody usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBe antigen with appearance of HBe antibody is consistent with resolution of HBV infectivity.

**Reference Values:** Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.


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**HBGCD 83626**

**Hepatitis Bs Antigen (HBsAg) for Cadaveric or Hemolyzed Specimens, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following HBV infection. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for >6 months indicates development of either a chronic carrier or chronic HBV infection.

**Useful For:** Testing cadaveric and hemolyzed blood specimens for hepatitis B surface antigen; FDA-licensed for use with hemolyzed specimens Diagnosis of acute, recent (<6 month duration), or chronic hepatitis B infection; determination of chronic hepatitis B carrier status

**Interpretation:** A positive result (reactive screening and confirmed positive by neutralization test; see Method Description) is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. A positive (confirmed) neutralization test result is considered the definitive test result for hepatitis B surface antigen (HBsAg). Specimens that are reactive by the screening test but negative (not confirmed) by the neutralization test are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg screening test results should be interpreted in conjunction with test results of other HBV serological markers (e.g., anti-hepatitis B surface antibody, anti-hepatitis B core total antibody). The presence of HBsAg is frequently associated with HBV infectivity, especially when accompanied by the presence of hepatitis Be antigen or HBV DNA.

**Reference Values:** Negative


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**HCSCR 63444**

**Hepatitis C Antibody Screen with Reflex to HCV RNA by PCR, Serum**

Current as of July 8, 2016 11:28 am CDT
Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-PCR (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur following resolution of infection. Current screening serologic tests to detect antibodies to HCV include EIA and chemiluminescence immunoassays. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. The following algorithms are available in Special Instructions: -Testing Algorithm for the Diagnosis of Hepatitis C Publications: Advances in the Laboratory Diagnosis of Hepatitis C (2002)

Useful For: Screening and detection of chronic hepatitis C virus infection in nonsymptomatic individuals Note: In accordance with National Coverage Determination guidance, this test is indicated for asymptomatic patients born from 1945 through 1965, those with history of injection drug use, or history of receiving blood transfusion prior to 1992.

Interpretation: Chemiluminescence Immunoassay: Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/CO) ratios of <8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm HCV antibody status. Reactive results with S/CO ratios of > or =8.0 are highly predictive (> or =95% probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA (HCVQU / Hepatitis C Virus [HCV] RNA Detection and Quantification by Real-Time Reverse Transcription-PCR [RT-PCR], Serum) is recommended for detection of HCV infection in such patients. RT-PCR: The quantification range of this test is 15 to 100,000,000 IU/mL. Negative results indicate that HCV RNA is not detected in the serum. A numerical result indicates the presence of HCV infection with active viral replication. Positive results with the comment of "HCV RNA detected, but <15 IU/mL" indicate that the HCV RNA present is at a level below the quantifiable lower limit of this assay. Follow-up testing by this assay is recommended in 1 to 3 months. Positive results with the comment of "but >100,000,000 IU/mL" indicate that the level of HCV RNA present is above the quantifiable upper limit of this assay. A single negative HCV RNA result with positive HCV antibody status (assay signal-to-cutoff ratio of > or =3.8 by EIA, or > or =8.0 by chemiluminescence immunoassay), does not necessarily indicate past or resolved HCV infection. Individuals with such results should be retested for HCV RNA in 1 to 2 months, to distinguish between patients with past or resolved HCV infection and those with chronic HCV infection having episodic HCV replication. Presence of HCV antibodies (assay signal-to-cutoff ratio of <3.8 by EIA or <8.0 by chemiluminescence immunoassay) in individuals with negative HCV RNA results may be confirmed by HCV Antibody Confirmation, Serum.

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

Hepatitis C Antibody with Reflex to HCV RNA by PCR, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-PCR (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur after resolution of infection. Current screening serologic tests to detect antibodies to HCV include EIA and chemiluminescence immunoassay. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: - There may be a long delay (up to 6 months) between exposure to the virus and the development of a detectable HCV antibody - False-reactive screening test result can occur - A reactive screening test result does not distinguish between past (resolved) and present HCV infection - Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. The following algorithms are available in Special Instructions: - Testing Algorithm for the Diagnosis of Hepatitis C

Publications: Advances in the Laboratory Diagnosis of Hepatitis C (2002)

Useful For: Detection and diagnosis of chronic hepatitis C virus infection in symptomatic patients

Interpretation: Chemiluminescence Immunoassay: Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/CO) ratios of <8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm anti-HCV status. Reactive results with S/CO ratios of > or =8.0 are highly predictive (> or =95% probability) of the true anti-HCV status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA (HCVQU / Hepatitis C Virus [HCV] RNA Detection and Quantification by Real-Time Reverse Transcription-PCR [RT-PCR], Serum) is recommended for detection of HCV infection in such patients. RT-PCR: The quantification range of this test is 15 to 100,000,000 IU/mL. Negative results indicate that HCV RNA is not detected in the serum. A numerical result indicates the presence of HCV infection with active viral replication. Positive results with the comment of "HCV RNA detected, but <15 IU/mL" indicate that the HCV RNA present is at a level below the quantifiable lower limit of this assay. Positive results with the comment of "but >100,000,000 IU/mL" indicate that the level of HCV RNA present is above the quantifiable upper limit of this assay. A single negative HCV RNA result with positive HCV antibody status (assay signal-to-cutoff ratio of > or =3.8 by EIA, or > or =8.0 by chemiluminescence immunoassay), does not necessarily indicate past or resolved HCV infection. Individuals with such results should be retested for HCV RNA in 1 to 2 months, to distinguish between patients with past or resolved HCV infection and those with chronic HCV infection having episodic HCV replication. Presence of anti-HCV antibodies (assay signal-to-cutoff ratio of <3.8 by EIA or <8.0 by chemiluminescence immunoassay) in individuals with negative HCV RNA results may be confirmed HCV Antibody Confirmation, Serum.
Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

Real-Time Reverse Transcription-PCR (RT-PCR), Serum

Clinical Information: Of all individuals infected with hepatitis C virus (HCV), about 75% of them will develop chronic hepatitis C with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or presence of detectable HCV RNA in serum or plasma. In patients with chronic HCV infection, the response to combined interferon-alpha and ribavirin therapy is correlated with pretreatment serum or plasma HCV RNA levels (viral load) and HCV genotype. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient’s pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks and/or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). To determine the duration of treatment and monitor the response to anti-HCV therapy, HCV RNA levels in serum or plasma are typically measured at 0 (baseline), 4 (rapid virologic response, RVR), 8, and 12 (early virologic response: EVR) weeks of therapy, end-of-treatment (24, 28, or 48 weeks depending on HCV genotype and treatment response), and 24 weeks post-treatment (sustained virologic response: SVR). The following algorithms are available in Special Instructions: -Testing Algorithm for the Screening and Diagnosis of Hepatitis C -Chronic Hepatitis C Treatment and Monitoring Algorithm: Interferon-Free Combination Therapy

Useful For: Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive) Monitoring disease progression in chronic HCV infection and/or response to anti-HCV therapy

Interpretation: This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. An "Undetected" result indicates that the HCV is absent in the patient’s serum specimen. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. To assess response-guided therapy eligibility, an "Undetected" result is required, and a result of "<15 IU/mL (<1.18 log IU/mL)" should not be considered equivalent to an "Undetected" result. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HCV viral replication in the patient. Monitoring HCV RNA levels over time is important to assess disease progression and/or monitoring a patient’s response to anti-HCV therapy. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result with the comment "Inconclusive" result. Submit a new specimen for testing if clinically indicated indicates that inhibitory substance(s) is/are present in the serum specimen tested. When clinically indicated, collection of a new serum specimen for retesting is recommended.

Reference Values:
Undetected


Hepatitis C Virus Antibody Confirmation, Serum

Clinical Information: Laboratory testing for hepatitis C virus (HCV) infection in patients and donors of organ, blood, cells, tissue, and tissue products usually begins by screening for the presence of HCV antibodies (anti-HCV) in serum, using an FDA-approved anti-HCV screening test. Specimens that are
repeatedly reactive by screening tests should be confirmed by more HCV-specific tests, such as direct
detection of HCV RNA by the reverse transcriptase-PCR (RT-PCR) or confirmatory detection of HCV
antibodies by serologic assays using recombinant HCV-specific antigens. In patients with reactive HCV
antibody screening test results but negative or undetectable HCV RNA test results, HCV antibody
confirmatory tests would be useful to distinguish between true- and false-reactive HCV antibody
screening test results. HCV antibodies are usually not detectable during the first 2 months following
infection, and they are usually detectable by the late convalescent stage (>6 months after onset) of
infection. These antibodies do not neutralize the virus, and they do not provide immunity against this viral
infection. Loss of HCV antibodies may occur in the years following resolution of infection. Despite the
value of serologic confirmation of HCV infection, several limitations of this test exist: -There may be a
long delay (up to 6 months) between exposure to the virus and development of detectable HCV
antibodies, especially in immunocompromised patients; -A positive test result does not distinguish
between past (resolved) and chronic HCV infection; -Serologic tests cannot predict or monitor response to
antiviral therapy Testing Algorithm for the Screening and Diagnosis of Hepatitis C is available in Special
Instructions.

**Useful For:** Confirming the presence of hepatitis C virus (HCV)-specific IgG antibodies in serum
specimens that are reactive by HCV antibody screening tests Distinguish between true- and false-reactive
HCV antibody screening test results

**Interpretation:** A positive result indicates the presence of hepatitis C virus (HCV)-specific IgG
antibodies due to past (resolved) or chronic hepatitis C. Past (resolved) HCV infection (accounting for
about 25% of all HCV-infected patients) can be distinguished from chronic HCV infection (about 75% of
all cases) only by direct detection of HCV RNA using molecular test methods (eg, HCVQU / Hepatitis C
Virus [HCV] RNA Detection and Quantification by Real-Time Reverse Transcription-PCR [RT-PCR],
Serum). HCV RNA is present in acute or chronic hepatitis C but not in past (resolved) HCV infection. A
negative result indicates absence of HCV-specific IgG antibodies. A reactive HCV antibody screening test
result with a negative HCV antibody confirmatory result indicates a probable false-reactive screening test
result. An indeterminate result indicates that HCV-specific IgG antibodies may or may not be present.
Indeterminate results should be interpreted along with patient's risk factors for HCV infection and clinical
findings. Individuals at risk for HCV infection with indeterminate results should be retested with an HCV
antibody confirmatory test in 1 to 2 months to determine the definitive HCV antibody status. Molecular
tests to detect HCV RNA may be necessary to determine HCV infection status in those at-risk
immunocompromised patients with indeterminate HCV antibody confirmatory test results due to delayed
appearance of fully complement of HCV-specific antibodies.

**Reference Values:**

- Negative

**Clinical References:**


**HCCDD 58127**

**Hepatitis C Virus Antibody in Cadaveric or Hemolyzed Specimens, Serum**

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of
post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United
States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. HCV
antibodies are usually not detectable during the early months following infection, but they are almost
always detectable by the late convalescent stage (>6 months after onset of acute infection). These
antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss
of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing are known: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. -False-reactive screening test results can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay (HCVL) for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric or hemolyzed serum specimens due to interference of heme with the nucleic acid amplification processes.

**Useful For:** Screening cadaveric or hemolyzed serum specimens for hepatitis C virus-specific IgG antibodies Note: This test is not intended for screening blood, cell, or tissue donors.

**Interpretation:** All specimens with signal-to-cutoff ratios of $>1.0$ will be considered reactive and reflexed to the hepatitis C virus (HCV) IgG antibody confirmatory test by line immunoassay (HCVL) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections ($<3$ months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

**Reference Values:**
Negative

**Clinical References:**

**HCCAD 87858**

**Hepatitis C Virus Antibody Screen for Cadaveric or Hemolyzed Specimens, Serum**

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. HCV antibodies are usually not detectable during the early months following infection, but they are almost always detectable by the late convalescent stage ($>6$ months after onset of acute infection). These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing are known: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. -False-reactive screening test results can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric or hemolyzed serum specimens due to interference of heme with the nucleic acid amplification processes.

**Useful For:** Screening cadaveric or hemolyzed serum specimens for hepatitis C virus infection in nonsymptomatic individuals Note: In accordance with National Coverage Determination guidance, this test is indicated for asymptomatic patients born from 1945 through 1965, those with history of injection drug use, or history of receiving blood transfusion prior to 1992.

**Interpretation:** All specimens with signal-to-cutoff ratios of $>1.0$ will be considered reactive and
reflex to the hepatitis C virus antibody confirmatory test by line immunoassay (HCVL) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

Reference Values:
Negative


Hepatitis C Virus Genotype, Serum

Clinical Information: Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the hepatitis C virus (HCV) genome allow classification of HCV into 6 major genotypes or clades (1 to 6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most commonly encountered HCV genotypes are 1a and 1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. Therefore, reliable methods for genotype determination are important for proper selection of antiviral therapy and optimal patient management. Infections with HCV genotypes 2 and 3 have better therapeutic response rates (80%-90%) than genotypes 1 and 4 (40%-50%) to previous standard combination therapy (ribavirin plus pegylated interferon alpha-2a or alpha-2b). Duration of such combination therapy is 24 weeks for chronic HCV genotype 2 and 3 infections in patients who show early virologic response (>2 log or 100-fold decrease in HCV RNA or no detectable HCV RNA at week 12 of therapy), while patients with chronic HCV genotype 1 and 4 infections receive a minimum of 48 weeks of such combination therapy if early virologic response is achieved (undetectable HCV RNA at week 4 of therapy). Therapeutic response rates for HCV genotype 1 infection are improved significantly (80%-90%) when oral direct acting antiviral agents (eg, simeprevir, sofosbuvir, ledipasvir + sofosbuvir, daclatasvir + sofosbuvir, omibitasvir + paritaprevir + ritonavir + dasabuvir) are added or used in lieu of interferon-based combination therapy. However, antiviral resistance can emerge during such combination therapy, and occurrence of such resistance is more frequent with HCV subtype 1a than 1b for simeprevir-treated patients. The American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C are available from URL: http://www.hcvguidelines.org/full-report-view The following algorithms are available in Special Instructions: - Testing Algorithm for the Screening and Diagnosis of Hepatitis C - Chronic Hepatitis C Treatment and Monitoring Algorithm: Interferon-Free Combination Therapy

Useful For: Determining hepatitis C virus genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Differentiating between hepatitis C virus subtypes 1a and 1b

Interpretation: An "Undetected" result indicates the absence of detectable hepatitis C virus (HCV) RNA in the specimen. An "Indeterminate" result may be due to one or more of the following causes: 1) low HCV RNA level (ie, <500 IU/mL), 2) HCV genotype 6; 3) probe reactivity with multiple HCV genotypes, or 4) variation in patientâ€™s HCV target sequences with mismatches to PCR primers and/or probes. Specimens generating indeterminate results with this assay will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum. A genotype result of "1" without a subtype result may be due to 1 or more of the following causes: 1) low HCV RNA level (ie, <500 IU/mL), 2) probe reactivity with multiple genotype 1 subtypes, or 3) variation in HCV genotype 1 target sequence. This assay is able to differentiate between HCV subtypes 1a and 1b. However, subtypes are not reported for HCV genotypes 2 to 5 due to limitations of the current genotyping assay in accurately differentiating the various subtypes of these genotypes. Results with multiple or mixed HCV genotypes (eg, 1, 5; 1a, 2; or 3, 5) may be due to mixed genotype infection or assay probe cross-reactivity. Only
those specimens with multiple or mixed genotype results containing genotype 1 but no subtype will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum.

**Reference Values:**
Undetected

**Clinical References:**

**FHED 91850**
**Hepatitis D Virus (HDV) IgM Antibody, EIA**

**Reference Values:**
Reference Range: Negative

**Interpretive Criteria:**

**Negative:** Antibody not detected

**Positive:** Antibody detected

HDV infection occurs only in association with HBV infection. Detection of HDV IgM indicates active HDV replication due to either acute infection or reactivation of chronic infection.

**FHEPD 91335**
**Hepatitis D Virus Antibody, Total**

**Reference Values:**
REFERENCE RANGE: Negative

**Interpretive Criteria:**

**NEGATIVE:** Antibody not detected

**EQUIVOCAL:** Submission of a second (collected 3 - 4 weeks after initial specimen) suggested if clinically warranted.

**POSITIVE:** Antibody detected

Hepatitis D virus (HDV) infection occurs in association with HBV infection. A positive result for HDV total antibody may indicate either acute or chronic HDV infection. HDV antibodies appear transiently during acute infection, and typically disappear with resolution of the infection. In contrast, HDV antibodies usually persist in chronic infection. Measurement of HDV IgM may help distinguish acute from chronic infection.

**HEVG 86211**
**Hepatitis E Virus IgG Antibody, Serum**

**Clinical Information:** Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, nonenveloped RNA virus is from animal reservoir (eg, hogs) to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the stool. In immunocompetent patients, viremia and virus shedding in the stool occur in the pre-icteric...
phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgG is the serologic test of choice to determine past exposure to HEV.

**Useful For:** Diagnosis of past exposure to hepatitis E virus

**Interpretation:** Positive results indicate past or resolved hepatitis E infection. Negative results indicate absence of previous exposure to hepatitis E virus (HEV). Borderline results may be seen in: 1) acute or recent hepatitis E infection with rising level of anti-HEV IgG, or 2) cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status.

**Reference Values:**
Negative

**Clinical References:**

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Hepatitis E Virus IgM Antibody Confirmation, Serum

**Clinical Information:** Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, nonenveloped RNA virus is from animal reservoirs (eg, hogs) and is transmitted to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the stool. In immunocompetent patients, viremia and virus shedding in the stool occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection. Positive predictive value of a given diagnostic laboratory test is dependent on the prevalence rate of the disease for which the test is being used. Screening tests for detection of diseases with low prevalence rates, such as acute hepatitis E, will have low positive predictive values (ie, relatively high rates of false-positive test results), despite having high specificity rates for such tests. Therefore, an HEV IgM antibody confirmatory test will be helpful and necessary to determine the true infection status of patients with reactive HEV IgM antibody screening test results.

**Useful For:** Confirmation of reactive hepatitis E virus IgM antibody screening test results for the diagnosis of acute or recent (<6 months) hepatitis E infection

**Interpretation:** Positive results confirm the presence of acute or recent (in the preceding 6 months) hepatitis E infection. Negative results indicate absence of acute or recent hepatitis E infection. Indeterminate results may be seen in: 1) acute hepatitis E infection with rising level of anti-hepatitis E virus (HEV) IgM; 2) recent hepatitis E infection with declining level of anti-HEV IgM; 3) acute hepatitis E infection due to HEV genotype 2 strains; or 4) cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgM and anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status. Unreadable results indicate the presence of unusually strong, nonspecific reactivity of the assay strip background that obscures proper reading of the bands. Such findings are usually due to nonspecific binding of non-hepatitis E IgM antibodies in patient’s serum to the HEVM antigens present on the assay strip. Repeat testing with anti-HEV IgM
Hepatitis E Virus IgM Antibody Screen with Reflex to Confirmation, Serum

Clinical Information: Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, non-enveloped RNA virus is transmitted from animal reservoirs (e.g., hogs) to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (e.g., months) of viremia and virus shedding in the stool. In immunocompetent patients, viremia and virus shedding in the stool occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection.

Useful For: Diagnosis of acute or recent (<6 months) hepatitis E infection

Interpretation: Positive results suggest the presence of acute or recent (in the preceding 6 months) hepatitis E infection. Reflex testing with HEVML / Hepatitis E Virus IgM Antibody Confirmation, Serum will be performed automatically. Negative results indicate absence of acute or recent hepatitis E infection. If clinical suspicion persists, submit new specimen for retesting in 1 to 2 weeks. Borderline results may be seen in: 1) acute hepatitis E infection with rising level of anti-hepatitis E virus (HEV) IgM; 2) recent hepatitis E infection with declining level of anti-HEV IgM; or 3) cross-reactivity with nonspecific antibodies (i.e., false-positive results). Reflex testing with HEVML / Hepatitis E Virus IgM Antibody Confirmation, Serum will be performed automatically.

Reference Values:
Negative

infection is spread primarily through percutaneous contact with infected blood products, e.g., blood transfusion, sharing of needles by drug addicts. The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients; some of these chronic carriers are asymptomatic. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products, or through other close, personal contacts. It is recognized as the cause of most cases of post-transfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV.

**Useful For:** Screening to determine a patient's previous exposure to hepatitis Determining immunity to hepatitis A and B Determining if a patient has been infected following exposure to an unknown type of hepatitis

**Interpretation:**
- Hepatitis A virus (HAV): Anti-HAV is usually detectable by the onset of symptoms (15-45 days after exposure). Serological diagnosis of acute HAV infection depends on the detection of IgM antibody and its presence indicates recent exposure and potential infectivity.
- Hepatitis B virus (HBV): Hepatitis B surface antigen (HBsAg) is the first serological marker present following HBV infection. A positive result is diagnostic of acute or chronic HBV infection and is associated with infectivity. In acute cases, HBsAg usually disappears 1 to 2 months following the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Hepatitis B core antibody (anti-HBc) IgM can be detected in serum shortly after the onset of symptoms and is usually present up to 6 months. Anti-HBc IgM may be the only serologic marker of a recent HBV infection and is detectable following the disappearance of HBsAg and prior to the appearance of hepatitis Bs antibody (anti-HBs) (i.e., core window period).
- Hepatitis C virus (HCV): Anti-HCV is usually not detectable during the early months of infection with HCV. A negative chemiluminescence immunoassay (CIA) antibody test result does not exclude the possibility of exposure to or infection with HCV. Negative results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent infections with HCV may have false-negative results due to the time required for seroconversion (an average of 8 to 9 weeks). If HCV infection is suspected, qualitative HCV RNA testing is recommended. See Advances in the Laboratory Diagnosis of Hepatitis C (2002) in Publications. The following algorithms are available in Special Instructions: 
  - HBV Infection-Diagnostic Approach and Management Algorithm 
  - Testing Algorithm for the Screening and Diagnosis of Hepatitis C 
  - Viral Hepatitis Serologic Profiles 

A positive CIA screen result suggests the presence of anti-HCV as a result of past or present HCV infection.

**Reference Values:**

**HEPATITIS A TOTAL ANTIBODIES**
- Negative

**HEPATITIS B SURFACE ANTIGEN**
- Negative

**HEPATITIS B SURFACE ANTIBODY**
- Unvaccinated: negative
- Vaccinated: positive

**HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE**
- Unvaccinated: <5.0 mIU/mL
- Vaccinated: ≥12.0 mIU/mL

**HEPATITIS B CORE TOTAL ANTIBODY**
- Negative

**HEPATITIS C VIRUS ANTIBODY**
- Negative

Current as of July 8, 2016 11:28 am CDT

Hepatitis Profile, Serum

Clinical Information: Hepatitis A: Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus, which is transmitted primarily by the fecal-oral route, is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral contact (with blood or oropharyngeal secretions) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus, or of newborns contracting HAV infection during delivery. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products, eg, blood transfusion, sharing of needles by drug addicts. The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients; some of these chronic carriers are asymptomatic.

Useful For: Screening to determine a patient's previous exposure or immunity to hepatitis A and B

Interpretation: Hepatitis A virus (HAV) infection: Anti-HAV is usually almost detectable by the onset of symptoms (15-45 days after exposure). Serological diagnosis of acute viral hepatitis A depends on the detection of IgM antibody and its presence indicates recent exposure and the possibility to be potentially infectious. Anti-HAV IgG rises quickly once the virus is cleared and persists for years. A positive anti-HAV (IgG and IgM) indicates that the patient has had either a recent or past HAV infection. Hepatitis B virus (HBV) infection: Hepatitis B surface antigen (HBsAg) is the first serological marker present following HBV infection. A positive result is diagnostic of acute or chronic hepatitis B infection and is associated with infectivity. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. In acute cases, HBsAg usually disappears 1 to 2 months following the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Hepatitis B core antibody (anti-HBc) IgM can be detected in serum shortly after the onset of symptoms and is usually present up to 6 months (ie, core window period). Anti-HBc IgM may be the only serologic marker of a recent hepatitis B infection detectable following the disappearance of HBsAg and prior to the appearance of anti-HBs. See Viral Hepatitis Serologic Profiles in Special Instructions.

Reference Values:

HEPATITIS B SURFACE ANTIGEN
Negative

HEPATITIS B CORE TOTAL ANTIBODY
Negative

HEPATITIS A ANTIBODY, IgG and IgM
Negative

HEPATITIS B SURFACE ANTIBODY
Unvaccinated: negative
Vaccinated: positive
HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE

Unvaccinated: <5.0 mIU/mL
Vaccinated: > or =12.0 mIU/mL

See Viral Hepatitis Serologic Profiles in Special Instructions.


HCCPR 62966

Hepatocellular Carcinoma Risk Panel

Clinical Information: Worldwide, hepatocellular carcinoma is the third leading cause of death from cancer.(1) While hepatocellular carcinoma can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of suspected hepatocellular carcinoma. However, increased serum concentrations of AFP might be found in chronic hepatitis and liver cirrhosis, as well as in other tumor types (eg, germ cell tumors[2]), decreasing the specificity of AFP testing for hepatocellular carcinoma. Furthermore, AFP is not expressed at high levels in all hepatocellular carcinoma patients, resulting in decreased sensitivity, especially in potentially curable small tumors. L3AFP: AFP is differentially glycosylated in several hepatic diseases. For example, UDP-alpha-1-->6-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation.(3) This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following electrophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP that is most closely associated with hepatocellular carcinoma is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP < or =200 ng/mL, which may result from a variety of benign pathologies, such as chronic liver diseases. DCP: Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many hepatocellular carcinoma (HCC) cells, and an abnormal prothrombin with all or some of unconverted glutamic acid is secreted. Therefore, this noncarboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to alpha fetoprotein AFP and AFP-L3% for assessing the risk of developing HCC. The elevation of both AFP-L3% and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3%, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3%, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion and/or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC.

Useful For: Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma

Interpretation: L3AFP: Alpha-fetoprotein (AFP)-L3 > or =10% is associated with a 7-fold increased
risk of developing hepatocellular carcinoma. Patients with AFP-L3 > or =10% should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. Total serum AFP >200 ng/mL is highly suggestive of a diagnosis of hepatocellular carcinoma. In patients with liver disease, a total serum AFP of >200 ng/mL is near 100% predictive of hepatocellular carcinoma. With decreasing total AFP levels, there is an increased likelihood that chronic liver disease, rather than hepatocellular carcinoma, is responsible for the AFP elevation. Based on a retrospective study at Mayo Clinic, for patients with total AFP levels < or =200 ng/mL, AFP-L3 specificity approaches 100% for hepatocellular carcinoma when its percentage exceeds 35% of the total AFP. (4) AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life. DCP: In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing hepatocellular carcinoma (HCC) is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%).

**Reference Values:**
- L3AFP: <10%
- DCP: <7.5 ng/mL

**Clinical References:**

**HER-2/neu, Quantitative, ELISA**

**Reference Values:**
- Reference Range: 0.0 - 15.0 ng/mL

**Clinical References:**

**HER2 Amplification Associated with Breast Cancer, FISH, Tissue**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: HER2 (ERBB2: c-erb-b2) is an oncogene on the long arm of chromosome 17 that is amplified in approximately 15% to 20% of breast cancers. Amplification or overexpression of HER2 has been shown to be associated with shorter disease-free survival and poorer overall survival in both node-negative and node-positive ductal breast cancers. Patients with HER2 gene amplification or overexpression are candidates for treatment with the drugs that target the human epidermal growth factor receptor 2 (HER2) protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab, lapatinib). FISH with labeled DNA probes to the pericentromeric region of chromosome 17 and to the HER2 locus can be used to determine if a patient’s breast cancer has HER2 gene amplification. Immunohistochemical analysis is used to determine if a tumor exhibits HER2 overexpression. FISH has been shown to be superior to Southern, Northern, and Western blots and immunohistochemical analyses for the determination of HER2 amplification in formalin-fixed, paraffin-embedded material. HER2 amplification as detected with FISH has been shown to be an independent predictor of poor clinical outcome.

Useful For: A prognostic indicator for patients with both node-positive or node-negative primary and metastatic breast cancer Guiding therapy, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib). Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 overexpression by immunohistochemistry

Interpretation: An interpretive report is provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines. Specimens with equivocal results as defined by 2013 ASCO/CAP guidelines will have reflex testing performed using the HER2/D17S122 probe set. The report will include a complete interpretation including the HER2:D17Z1 and HER2:D17S122 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural changes that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values: An interpretive report will be provided.

**Clinical Information:** Gastroesophageal cancer is the fourth most commonly diagnosed cancer. To date, chemotherapy for gastroesophageal cancer is often ineffective and its prognosis remains poor. Recent studies suggest that the HER2 oncogene can be used as a marker to identify aggressive disease. In much the same way as was demonstrated for HER2-positive breast cancer, the HER2 gene status in gastroesophageal cancers can be used to determine treatment approaches. Amplification of the HER2 gene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastric-esophageal junction cancers. Patients whose tumors demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab, lapatinib).

**Useful For:** Guiding therapy for patients with primary or metastatic gastroesophageal tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 overexpression by immunohistochemistry

**Interpretation:** An interpretive report is provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors, and the guidelines used by the ToGA trial. Specimens with equivocal results as defined by 2013 ASCO/CAP guidelines will have reflex testing performed using the HER2/D17S122 probe set. The report will include a complete interpretation including the HER2:D17Z1 and HER2:D17S122 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural changes that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**H2URF 35850**

**HER2 Amplification Associated with Urothelial Carcinoma, FISH, Tissue**

**Clinical Information:** Human epidermal growth factor receptor 2 (HER2) plays a fundamental role in cell growth, survival, and migration. The assessment of HER2 gene status is crucial for the management of breast cancer. Studies have shown that HER2 is also expressed in a proportion of urothelial carcinoma of the urinary bladder (UCB), making it a potential target for UCB therapy. HER2-positive gene status is associated with aggressive UCB and provides independent prognostic information. Assessment of HER2 status may be used to identify patients at high risk of disease progression.
**Useful For:** Guiding therapy for patients with primary or metastatic urothelial tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib). Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry.

**Interpretation:** An interpretive report is provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors. Specimens with equivocal results as defined by 2013 ASCO/CAP guidelines will have reflex testing performed using the HER2/D17S122 probe set. The report will include a complete interpretation including the HER2:D17Z1 and HER2:D17S122 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural changes that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

**Reference Values:**

An interpretative report will be provided.

**Clinical References:**


**HER2 Amplification, Miscellaneous Tumor, FISH, Tissue**

**Clinical Information:** Amplification of the HER2 oncogene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival and poorer overall survival in some cancers. Patients whose breast or gastroesophageal cancers demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab, lapatinib).

**Useful For:** Guiding cancer therapy, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib). Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry.

**Interpretation:** An interpretive report is provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors. Specimens with equivocal results as defined by 2013 ASCO/CAP guidelines will have reflex testing performed using the HER2/D17S122 probe set. The report will include a complete interpretation including the HER2:D17Z1 and HER2:D17S122 results. The degree of HER2 amplification varies in tumors. Some exhibit a high level of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have a similar prognosis or response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural changes.
that increase HER2 copy number. Rare cases may not show HER2 amplification but have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and may be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values:
An interpretative report will be provided.


HER2, Breast, Quantitative Immunohistochemistry, Automated

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections. This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer.

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values: Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.


HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

Useful For: Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections.

Interpretation: Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or...
negative (0 or 1+). Equivocal (2+) cases will automatically reflex to H2GEF / HER2 Amplification Associated with Gastroesophageal Cancer, FISH, Tissue at an additional charge.

**Reference Values:**
Reported as negative (0, 1+), equivocal (2+), and positive (3+)

**Clinical References:**

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**COLAB** 35382  
**Hereditary Colon Cancer CGH Array**

**Reference Values:**
Only orderable as a reflex. For further information see:
- AXINZ / AXIN2 Gene, Full Gene Analysis
- BMPRZ / BMPR1A Gene, Full Gene Analysis
- CHEKZ / CHEK2 Gene, Full Gene Analysis
- MLH3Z / MLH3 Gene, Full Gene Analysis
- PTENZ / PTEN Gene, Full Gene Analysis
- SMADZ / SMAD4 Gene, Full Gene Analysis
- STKZ / STK11 Gene, Full Gene Analysis
- TP53Z / TP53 Gene, Full Gene Analysis
- CDH1Z / CDH1 Gene, Full Gene Analysis
- M1M2Z / MLH1/MSH2 Genes, Full Gene Analysis
- MLH1Z / MLH1 Gene, Full Gene Analysis
- MSH2Z / MSH2 Gene, Full Gene Analysis
- MSH6Z / MSH6 Gene, Full Gene Analysis
- APCZ / APC Gene, Full Gene Analysis

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**HCRC** 35450  
**Hereditary Colon Cancer Multi-Gene Panel**

**Clinical Information:** Colorectal cancer occurs in approximately 5% to 6% of individuals in the general population. In rare cases, individuals with a family history of colorectal cancer may be at increased risk for colon and other cancers due to a single-gene predisposition syndrome, known as hereditary colorectal cancer. The 2 most common hereditary colorectal cancer syndromes are Lynch syndrome and familial adenomatous polyposis (FAP). However, there are multiple other genes which are also known to cause to hereditary colorectal cancer or contribute to an increased risk for colorectal cancer. This panel uses next generation sequencing (NGS), array comparative genomic hybridization (aCGH), and other technologies to evaluate for germline mutations in 17 genes known to be associated with an increased risk for colon cancer development. Two of the genes listed, CHEK2 and MLH3, are not associated with a known hereditary cancer syndrome defined by a distinct spectrum of tumors. However, literature suggests that mutations in these genes may confer an increased risk for colon cancer and therefore are predicted to contribute to cancer risk in patients and families. Gene Known Association
- MLH1 Lynch syndrome
- MSH2 Lynch syndrome
- MSH6 Lynch syndrome
- PMS2 Lynch syndrome
- EPCAM Lynch syndrome
- APC Familial adenomatous polyposis
- MYH/MutYH MYH-associated polyposis
- SCG5/GREM1 Hereditary mixed polyposis syndrome
- STK11 Peutz-Jeghers syndrome
- SMAD4 Juvenile polyposis syndrome
- BMPR1A Juvenile polyposis syndrome
- PTEN PTEN hamartoma tumor syndrome
- CDH1 Hereditary diffuse gastric cancer
- AXIN2 Oligodontia-colorectal cancer syndrome
- CHEK2 Low-risk gene MLH3 Low-risk gene

**Indications for testing include but are not limited to:**
- Patients in whom no specific colorectal cancer syndrome is evident but for whom there is a clear familial component
- Patients whose family history is consistent with familial colorectal cancer type X
- Patients with a strong suspicion for a single-gene hereditary colon cancer syndrome based on an autosomal dominant pattern of colon cancer in the family
- Patients with a personal or family history of colonic polyposis

Current as of July 8, 2016 11:28 am CDT
Useful For: Providing a comprehensive evaluation for hereditary colon cancer in patients with a personal or family history suggestive of a hereditary colon cancer syndrome. Serving as a second-tier test for patients in whom previous targeted gene mutation analyses for specific hereditary colorectal cancer-related genes were negative. Establishing a diagnosis of a hereditary colon cancer syndrome in some cases, allowing for targeted cancer surveillance of associated extra-colonic organs known to be at increased risk for cancer. Identifying mutations within genes known to be associated with increased risk for colon cancer allowing for predictive testing of at-risk family members.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Clinical References:

Hereditary Erythrocytosis Mutations

Clinical Information: Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera or PV), or secondary, in response to increased serum erythropoietin (Epo) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by mutations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to...
increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Markedly Increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (official name EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (official name EGLN1) gene. Mutations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of mutations, in PHD2 and HIF2A, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating mutations in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to Epo hypersensitivity. All currently known mutations have been localized to exon 8, are mainly missense or small deletion and insertions resulting in stop codons, and are heterozygous. EPOR mutations are associated with decreased to normal Epo levels and normal p50 values (see Table).

**Useful For:** The definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

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**Hereditary Hemorrhagic Telangiectasia, ACVRL1 Gene, Known Mutation**

**Clinical Information:** Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVMs) of the skin, mucosa, and viscera. Small AVMs, or telangiectasias, develop predominantly on the face, oral cavity, and/or hands, and spontaneous, recurrent epistaxis (nosebleed) is a common presenting sign. Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of
larger AVMs, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively. HHT is inherited in an autosomal dominant manner; most individuals have an affected parent. HHT occurs with wide ethnic and geographic distribution, and it is significantly more frequent than formerly thought. It is most common in Caucasians, but it occasionally occurs in Asians, Africans, and individuals of Middle Eastern descent. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, and 80% to 90% by age 21 years. As many as 90% to 95% of affected individuals eventually develop recurrent epistaxis. Two genes are most commonly associated with HHT: the endoglin gene (ENG), containing 15 exons and located on chromosome 9 at band q34; and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1), containing 10 exons and located on chromosome 12 at band q1. Mutations in these genes occur in about 80% of individuals with HHT. ENG and ACVRL1 encode for membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Mutations in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVMs, whereas ACVRL1 mutations occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVMs. It has been suggested that HHT1 has a more severe phenotype compared to HHT2. ACVRL1 gene known mutation testing is for the genetic testing of individuals who are at risk for an ACVRL1 mutation that has been previously identified in the family. If the familial mutation is not known, the familial proband should be screened for ENG and ACVRL1 mutations via full gene analyses (HHTP / Hereditary Hemorrhagic Telangiectasia, ENG and ACVRL1 Full Gene Analysis). Once a mutation has been identified in a family, known mutation analysis can be performed in at-risk family members. HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing for ENG and ACVRL1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of HHT diagnosis will allow for proper treatment and management of the disease, preconception/prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening.(1)

Useful For: Genetic testing of individuals at risk for a known activin A receptor, type II-like 1 (ACVRL1) familial mutation (associated with hereditary hemorrhagic telangiectasia)

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


HHTP

Hereditary Hemorrhagic Telangiectasia, ENG and ACVRL1 Full Gene Analysis

Clinical Information: Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVMs, or telangiectasias, develop predominantly on the face, oral cavity, and/or hands, and spontaneous, recurrent epistaxis (nosebleed) is a common presenting sign. Symptomatic telangiectasias occur in the
gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of larger AVMs, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively. HHT is inherited in an autosomal dominant manner; most individuals have an affected parent. HHT occurs with wide ethnic and geographic distribution, and is significantly more frequent than formerly thought. It is most common in Caucasians, but it occasionally occurs in Asians, Africans, and individuals of Middle Eastern descent. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, and 80% to 90% by age 21 years. As many as 90% to 95% of affected individuals eventually develop recurrent epistaxis. Two genes are most commonly associated with HHT: the endoglin gene (ENG), containing 15 exons and located on chromosome 9 at band q34; and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1), containing 10 exons and located on chromosome 12 at band q1. Mutations in these genes occur in about 80% of individuals with HHT. ENG and ACVRL1 encode for membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Mutations in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVMs, whereas ACVRL1 mutations occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVMs. It has been suggested that HHT1 has a more severe phenotype compared to HHT2. The majority of mutations in ENG and ACVRL1 are point mutations, which are detectable by sequencing. Sequencing of ENG and ACVRL1 provides for a detection rate of approximately 60% to 80% of mutations involved in HHT. Approximately 10% of ENG and ACVRL1 mutations are large genomic deletions and duplications (also known as dosage alterations), which are not detectable by sequencing, but are detectable by methods such as multiplex ligation-dependent probe amplification (MLPA). HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing for ENG and ACVRL1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of HHT diagnosis will allow for proper treatment and management of the disease, preconception/prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening.(1)

Useful For: Aiding in the diagnosis of hereditary hemorrhagic telangiectasia, types 1 and 2

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

Telangiectasias, develop predominantly on the face, oral cavity, and/or hands, and spontaneous, recurrent epistaxis (nosebleeds) is a common presenting sign. Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of larger AVMs, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively. HHT is inherited in an autosomal dominant manner; most individuals have an affected parent. HHT occurs with wide ethnic and geographic distribution, and it is significantly more frequent than formerly thought. It is most common in Caucasians, but it occasionally occurs in Asians, Africans, and individuals of Middle Eastern descent. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetration seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, and 80% to 90% by age 21 years. As many as 90% to 95% of affected individuals eventually develop recurrent epistaxis. Two genes are most commonly associated with HHT: the endoglin gene (ENG), containing 15 exons and located on chromosome 9 at band q34; and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1), containing 10 exons and located on chromosome 12 at band q1. Mutations in these genes occur in about 80% of individuals with HHT. ENG and ACVRL1 encode for membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Mutations in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVMs, whereas ACVRL1 mutations occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVMs. It has been suggested that HHT1 has a more severe phenotype compared to HHT2. Approximately 10% of ENG and ACVRL1 mutations are large genomic deletions and duplications (also known as dosage alterations), which are detectable by methods such as multiplex ligation-dependent probe amplification (MLPA). The majority of mutations in ENG and ACVRL1 are point mutations, which are detectable by sequencing and provide for a detection rate of approximately 60% to 80% of mutations involved in HHT. HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing for ENG and ACVRL1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of HHT diagnosis will allow for proper treatment and management of the disease, preconception/prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening.(1)

**Useful For:** Aiding in the diagnosis of hereditary hemorrhagic telangiectasia, types 1 and 2

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**ENGK**

**Hereditary Hemorrhagic Telangiectasia, ENG Gene, Known Mutation**

**Clinical Information:** Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the
presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVMs, or telangiectasias, develop predominantly on the face, oral cavity, and/or hands, and spontaneous, recurrent epistaxis (nosebleed) is a common presenting sign. Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of larger AVMs, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively. HHT is inherited in an autosomal dominant manner; most individuals have an affected parent. HHT occurs with wide ethnic and geographic distribution, and it is significantly more frequent than formerly thought. It is most common in Caucasians, but it occasionally occurs in Asians, Africans, and individuals of Middle Eastern descent. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, and 80% to 90% by age 21 years. As many as 90% to 95% of affected individuals eventually develop recurrent epistaxis. Two genes are most commonly associated with HHT: the endoglin gene (ENG), containing 15 exons and located on chromosome 9 at band q34; and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1), containing 10 exons and located on chromosome 12 at band q1. Mutations in these genes occur in about 80% of individuals with HHT. ENG and ACVRL1 encode for membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Mutations in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVMs, whereas ACVRL1 mutations occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVMs. It has been suggested that HHT1 has a more severe phenotype compared to HHT2. ENG gene, known mutation testing is for the genetic testing of individuals who are at risk for an ENG mutation that has been previously identified in the family. If the familial mutation is not known, the familial proband should be screened for ENG and ACVRL1 mutations via full gene analyses (HTTP / Hereditary Hemorrhagic Telangiectasia, ENG and ACVRL1 Full Gene Analysis). Once a mutation has been identified in a family, known mutation analysis can be performed in at-risk family members. HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing for ENG and ACVRL1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of HHT diagnosis will allow for proper treatment and management of the disease, preconception/prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening.(1)

**Useful For:** Genetic testing of individuals at risk for a known endoglin gene (ENG) familial mutation (associated with hereditary hemorrhagic telangiectasia)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Clinical Information: Inherited peripheral neuropathies are a diverse group of disorders with heterogeneous genetic causes that can be divided into major categories based on the pattern of inheritance and nerve conduction studies. Hereditary motor and sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT) disease, is a major category of inherited peripheral neuropathies and is the most commonly inherited neuromuscular disorder. It is characterized by the motor and/or sensory peripheral nerve involvement. The clinical phenotype is variable, and includes wasting and weakness of the distal limb muscles, skeletal deformities, and hearing loss. HMSN/CMT is classified into 5 groups: 1) HMSN 1, which is a dominantly inherited demyelinating form; 2) HMSN 2, a dominantly inherited axonal predominant neuropathy; 3) HMSN 3 (also called Dejerine-Sottas disease), which is often inherited dominantly, with onset in infancy or childhood and is characterized by extremely slow nerve conduction velocities resulting in loss of ambulatory milestones and more generalized neurologic deficit; 4) HMSN 4, an autosomal recessive inherited demyelinating form that may also present with extraneural features, including facial dysmorphism and scoliosis, particularly those with HMSN 4C, the most frequent form of HMSN 4; 5) HMSN 5, a form associated with spasticity, also known as "complex hereditary spastic paraplegia (HSP)." Given the considerable phenotypic and genetic heterogeneity of HSMN/CMT disease, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this group of inherited peripheral neuropathies. The recommended first-tier test to screen for hereditary motor and sensory neuropathy is PMP22 / PMP22, Peripheral Neuropathy, FISH, which assess for large deletions and duplications of the PMP22 gene. See Targeted Genes Interrogated by Motor and Sensory Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

Useful For: Diagnosis of hereditary motor and sensory neuropathy (HMSN) or Charcot-Marie-Tooth (CMT) disease associated with known causal genes. Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary motor and sensory neuropathy-related genes were negative. Identifying mutations within genes known to be associated with inherited hereditary motor and sensory neuropathy, allowing for predictive testing of at-risk family members.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Hereditary Motor Neuropathy Panel by Next-Generation Sequencing (NGS)

Clinical Information: Inherited peripheral neuropathies are a relatively common, diverse group of disorders with heterogeneous genetic causes. Based on the pattern of inheritance and nerve conduction studies, inherited peripheral neuropathies with isolated nerve involvement can be divided into major categories. Distal hereditary motor neuropathies (dHMN) are one of the major categories of peripheral inherited neuropathies and are characterized by length-dependent, slowly progressive motor neuropathies with variable nerve conduction velocities. The clinical phenotype is variable, but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. There is significant phenotypic overlap with hereditary motor sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT); however, sensory loss is usually absent in dHMN. dHMN are subdivided into 11 subtypes based on inheritance pattern and clinical features and include types 1-7. dHMN plus pyramidal signs, X-linked, congenital distal SMA, and Jerash type. Given the considerable phenotypic and genetic heterogeneity of dHMN, a comprehensive diagnostic genetic test is helpful to establish the genetic cause in this group of inherited neuropathies. See Targeted Genes Interrogated by Hereditary Motor...
Motor Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosing distal hereditary motor neuropathy (dHMN) associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary motor neuropathy-related genes were negative Identifying mutations within genes known to be associated with inherited hereditary motor neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**HPPAN 35640**

**Hereditary Pancreatitis Panel**

**Clinical Information:** Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. PRSS1: Hereditary pancreatitis (HP) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations. The most common monogenic cause of HP is the presence of a mutation in the cationic trypsinogen (PRSS1) gene. Mutations in the PRSS1 gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced or tropical pancreatitis. Although several mutations have been identified, the R122H, N29I, and A16V mutations are the most common disease-causing mutations in PRSS1 associated with HP. Data suggests that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%. SPINK1: Biallelic mutations in the SPINK1 gene have been associated with increased susceptibility to chronic pancreatitis especially in families without PRSS1 mutations; however, it is unknown if biallelic mutations alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous SPINK1 mutations appear to modify disease severity when observed in combination with mutations in other genes. Unlike PRSS1 mutations, SPINK1 mutations have been associated with alcohol-induced and tropical pancreatitis. CFTR: Pancreatitis is a known manifestation of an atypical CFTR-related disorder in which 2 mutations in the CFTR gene are identified. However, CFTR mutations can also co-occur with mutations in CTRC, SPINK1, or CASR to confer pancreatitis disease susceptibility. When observed in the context of a SPINK1 mutation, for example, heterozygous mutations in CFTR are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population. CTRC: Mutations in CTRC have been observed in individuals with chronic pancreatitis in association with other risk factors such as mutations in CFTR or SPINK1 or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of CTRC mutations in the context of other risk factors as opposed to CTRC mutations alone.

**Useful For:** Confirmation of suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis Identification of gene mutations contributing to pancreatitis in an individual or family Identification of gene mutations to allow for predictive and diagnostic testing in
**Family Members**

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Hereditary Sensory/Autonomic Neuropathy Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Based on the pattern of inheritance and nerve conduction studies, inherited peripheral neuropathies with isolated nerve involvement can be divided into major categories. Hereditary sensory and autonomic neuropathies (HSAN), or hereditary sensory neuropathies (HSN) if autonomic dysfunction is absent, is one of these major categories of inherited peripheral neuropathies. They affect sensory and autonomic nerves and the hallmark feature is the presence of prominent small-fiber involvement. HSAN are subdivided into 5 groups based on age of onset, inheritance pattern, and clinical features: HSAN 1 varieties (HSAN 1A-E) follow an autosomal dominant inheritance pattern with juvenile or adult onset, and severe sensory loss and autonomic dysfunction; HSAN 2-5 have an autosomal recessive inheritance pattern and are usually congenital; HSAN3, also known as familial dysautonomia or Rilay-Day syndrome, is characterized by prominent autonomic and small-fiber sensory involvement; HSAN 4 and 5 are characterized by insensitivity to pain and widespread autonomic disturbance, with HSAN 4 also featuring mental retardation. Given the considerable phenotypic and genetic heterogeneity of HSAN/HSN, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this group of inherited neuropathies. See Targeted Genes Interrogated by Hereditary Sensory Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosis of inherited hereditary sensory (HSN) and autonomic neuropathy (HSAN) associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary motor and sensory neuropathy-related genes were negative Identifying mutations within genes known to be associated with inherited hereditary motor and sensory neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Hereditary Spastic Paraplegia Neuropathy Panel by Next-Generation Sequencing (NGS)

Clinical Information: Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Hereditary spastic paraplegia (HSP) is characterized by progressive lower extremity weakness and spasticity, and may present with prominent peripheral neuropathy as one of the complicated forms, also known as hereditary motor sensory neuropathy 5 (HMSN 5). The complicated forms are associated with a variety of other neurological systemic abnormalities and usually follow an autosomal recessive inheritance pattern. The uncomplicated or pure form presents with lower limb weakness and spasticity, and is predominantly characterized by an autosomal dominant inheritance pattern. Given the considerable phenotypic and genetic heterogeneity of HSP, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this HSP with neuropathy. See Targeted Genes Interrogated by Spastic Paraplegia Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

Useful For: Diagnosis of hereditary spastic paraplegia with neuropathy associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary spastic paraplegia-related genes were negative Identifying mutations within genes known to be associated with hereditary spastic paraplegia, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV), Molecular Detection, PCR

Clinical Information: Herpes simplex virus (HSV) causes various clinical syndromes. Anatomic sites infected include skin, lips and oral cavity, eyes, genital tract, and central nervous system. Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before age 10. After primary infection with VZV, the virus persists in latent form and may emerge (usually in adults age 50 and older) clinically to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

Useful For: Rapid diagnosis of herpes simplex virus and varicella-zoster virus infections

Interpretation: Herpes Simplex Virus (HSV) PCR: This is a qualitative assay; results are reported either as negative or positive for HSV type 1 or HSV type 2. In a small number of cases (eg, <1%), HSV is detected but this assay may not be able to provide a definitive subtype (HSV-1 versus HSV-2). This is due to mutations in the region of the HSV genome to which the PCR probes bind. When this result is observed, the report will go out as “Indeterminate”, which means that HSV DNA was detected, but the
Herpes Simplex Virus (HSV) Antibody Screen, IgM, by EIA, Serum

Clinical Information: The herpesvirus family contains herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesviruses 6 through 8. HSV types 1 and 2 produce infections that are expressed in various clinical manifestations ranging from mild stomatitis to disseminated and fatal disease. The more common clinical conditions include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 1 is closely associated with infections of the mouth and lips, although genital infections can be common in some populations. HSV type 2 is the cause of the majority of urogenital infections and is almost exclusively found in adults.

Useful For: Aiding in the diagnosis of infection with herpes simplex virus

Interpretation: A positive result (ie, the presence of IgM class herpes simplex virus [HSV] 1 and/or 2 antibodies) indicates recent infection. The presence of HSV 1 and/or 2 antibodies may indicate a primary or reactivated infection, but cannot distinguish between them. Specimens with positive results are automatically tested for IgM antibodies by a second method (immunofluorescence assay [IFA]). The continued presence or level of antibody cannot be used to determine the success or failure of therapy. The prevalence of HSV IgM antibodies can vary depending on a number of factors such as age, gender, geographical location, socio-economic status, race, sexual behavior, testing method used, specimen
collection and handling procedures, and the clinical and epidemiological history of individual patients. A negative result does not necessarily rule out a primary or reactivated infection since specimens may have been collected too early in the course of disease, when antibodies have not yet reached detectable levels, or too late, after IgM levels have declined below detectable levels.

**Reference Values:**
Negative (reported as reactive or negative)

**Clinical References:**

**HSMR**

Herpes Simplex Virus (HSV) Antibody, IgM, by Immunofluorescence Assay (IFA), Serum

**Reference Values:**
Only orderable as part of either TRCHM / Torch Profile IgM, Serum or MHSV / Herpes Simplex Virus (HSV) Antibody Screen, IgM, by EIA, Serum.

**HSVG**

Herpes Simplex Virus (HSV) Type 1- and Type 2-Specific Antibodies, IgG, Serum

**Clinical Information:** Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. (1) For example, the likelihood of reactivation of the infection (type 2 -> type 1) and the method of antiviral therapy may differ depending on the specific type of HSV causing disease. In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery. (2-3)

**Useful For:** Determining whether a patient has been previously exposed to herpes simplex virus (HSV) types 1 and 2 Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

**Interpretation:** This assay detects IgG-class antibodies to type-specific herpes simplex virus (HSV) glycoprotein G (gG), and may allow for the differentiation of infection caused by HSV types 1 and 2. The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

**Reference Values:**
Negative (reported as positive, negative, or equivocal)

**Clinical References:**
Herpes Simplex Virus (HSV) Type 1- and Type 2-Specific Antibodies, Serum

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 differ significantly in their disease manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus may occur in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. For example, the likelihood of reactivation of the infection (type 2 > type 1) and the method of antiviral therapy may be different depending on the specific type of HSV causing disease. In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.

Useful For: Supplementing culture or molecular detection of herpes simplex virus (HSV) for the diagnosis of acute infection Determining whether a patient has been previously exposed to HSV types 1 or 2 Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

Interpretation: The presence of IgM herpes simplex virus (HSV) antibodies indicates acute infection with either HSV type 1 or 2. The IgG antibody assay detects IgG-class antibodies to type-specific HSV glycoprotein G (gG), and may allow for the differentiation of infection caused by HSV types 1 and 2. The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

Reference Values:

HSV TYPE 1 ANTIBODY, IgG
Negative (reported as positive, negative, or equivocal)

HSV TYPE 2 ANTIBODY, IgG
Negative (reported as positive, negative, or equivocal)

HSV ANTIBODY SCREEN, IgM, by EIA
Negative (reported as reactive or negative)

Herpes Simplex Virus (HSV), Culture From Neonates

**Clinical Information:** Herpes simplex virus (HSV) types 1 (HSV-1) and 2 (HSV-2) cause various clinical syndromes. Anatomic sites infected include the skin, oral mucosa, oral cavity, eyes, genital tract, and central nervous system (CNS). Systemic involvement may also occur. HSV infections are common, with data suggesting that the seroprevalence of HSV-1 and HSV-2 in the United States (2005-2010) is 53.9% and 15.7%, respectively. Although HSV-1 has historically been believed to cause recurrent oral lesions, it is an increasingly important cause of genital herpes. Both HSV-1 and HSV-2 can cause CNS disease, with infection in neonates being considered a medical emergency. Diagnostic methods for HSV have included routine viral culture, molecular testing by PCR, and serology. It is difficult to recover HSV from cerebrospinal fluid (CSF) specimens using viral culture, and the serologic diagnosis of HSV is limited by the inability to distinguish between primary and reactivated disease. Detection of HSV by real-time PCR is now recognized as the most sensitive approach to diagnose HSV infection, especially CNS-associated HSV disease. However, performing viral culture for HSV in neonates being evaluated for potential congenital herpes is still recommended.

**Useful For:** An aid in the diagnosis of congenital herpes simplex virus (HSV) infection through the recovery of HSV using viral culture (shell-vial)

**Interpretation:** Recovery of herpes simplex virus (HSV) from clinical specimens supports the diagnosis of congenital infection due to the virus. A negative result by rapid culture should be interpreted in the context of the patient’s clinical presentation and exposure history. Furthermore, testing by real-time PCR for this virus should be considered prior to ruling out HSV disease.

**Reference Values:**
No virus isolated

**Clinical References:**

Herpes Simplex Virus (HSV), Molecular Detection, PCR

**Clinical Information:** Herpes simplex virus (HSV) causes various clinical syndromes. Anatomic sites infected include skin, lips, oral cavity, eyes, genital tract, and central nervous system (CNS). Systemic involvement may also occur. Fresh brain tissue is the definitive specimen for detection of HSV from patients with CNS disease. However, because brain biopsy is an invasive procedure, it is infrequently performed for laboratory diagnosis. Similarly, it is difficult to recover HSV from cerebrospinal fluid (CSF) specimens in culture systems, and the serologic diagnosis of HSV CNS disease has not been informative during early onset disease. HSV PCR detection from CSF is a sensitive and specific alternative for detection of disease involving the CNS, as well as oral, genital, ocular, and other sites.

**Useful For:** Aiding in the rapid diagnosis of herpes simplex virus (HSV) infections, including qualitative detection of HSV DNA in cerebrospinal fluid and other (non-blood) clinical specimens

**Qualitative detection of HSV DNA**

**Interpretation:** This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2. In a small number of cases (eg, <1%), HSV is detected but
Herpes Simplex Virus (HSV), Molecular Detection, PCR, Blood

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 cause a variety of clinical syndromes. Anatomic sites infected include the skin, lips, oral cavity, eyes, genital tract, and central nervous system (CNS). Systemic disease may also occur, in which the virus may be detectable in the bloodstream. The detection of HSV-1 or HSV-2 from the blood may help support the diagnosis of disseminated disease associated with this virus.

Useful For: An aid in the rapid diagnosis of disseminated disease due to herpes simplex virus (HSV) Qualitative detection of HSV DNA

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2. In a small number of cases (eg, <1%), HSV is detected but this assay may not be able to provide a definitive subtype (HSV-1 versus HSV-2). This is due to mutations in the region of the HSV genome to which the PCR probes bind. When this result is observed, the report will go out as "Indeterminate", which means that HSV DNA was detected, but the assay was unable to provide a specific subtype. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:
HSV-1: negative
HSV-2: negative

Clinical References:
FHERV 57305  Herpes Simplex Virus by PCR
Reference Values:
Not Detected

This test is pursuant to an agreement with Roche Molecular Systems, Inc.

FHHV6 91311  Herpes Virus 6 DNA, Qualitative Real-Time PCR
Reference Values:
Reference Range: Not Detected

FHV6D 57484  Herpes Virus-6 DNA, Quantitative Real-Time PCR
Reference Values:
<500 copies/mL

FHP6 80419  Herpesvirus 6 Antibodies (IgG, IgM)
Reference Values:
REFERENCE RANGE: IgG <1:10
IgM <1:20

Human Herpesvirus 6 (HHV-6) infects T-lymphocytes, and has been identified as an etiologic agent of exanthema subitum. Rises in antibody titers to HHV-6 have been detected during infection with other viruses. In seroepidemiology studies of the prevalence of exposure using serum screening dilutions of 1:10, the detection of IgG antibody in a mid-life population approaches 100%. Due to this high prevalence of HHV-6 antibody, correlations of single IgG titers with specific diseases are of little clinical value.

Evidence of acute infection or reactivation of HHV-6 is demonstrated by a significant rise or seroconversion of IgG and IgM titers.

FHV7D 57372  Herpesvirus 7 (HHV-7) DNA, Quantitative Real-Time PCR
Reference Values:
Reference Range: <500 copies/mL

FH7GM 57487  Herpesvirus 7 IgG and IgM Antibody Panel, IFA
Reference Values:
Reference Range:

IgG <1:320
IgM <1:20

Human Herpesvirus 7 (HHV-7), a close relative of HHV-6, is found in >85% of the population, with transmission occurring in early childhood. Like HHV-6, HHV-7 is a cause of exanthem subitum (roseola infantum). Due to the ubiquitous nature of HHV-7 infection, >80% of individuals in the general population exhibit HHV-7 IgG titers >or=1:20; however, only 5% of these individuals exhibit titers >1:320. Thus, HH-7 IgG titers > or = 1:320 are suggestive of recent HHV-7 infection. Detection of HHV-7 specific IgM is also indicative of recent infection.
**Herpesvirus 8 (HHV-8) DNA, Quantitative Real-Time PCR**

**Reference Values:**
Reference Range: <1000 copies/mL

**Herring, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Hexagonal Phospholipid Neutralization**

**Reference Values:**

<8 sec

This is a qualitative assay and is therefore reported as positive for
lupus anticoagulant or negative. The quantitative value is provided as an aid in diagnosis.

Test Performed by: Esoterix Coagulation
8490 Upland Dr.
Suite 100
Englewood, CO 80112

**HEXAI**

**82397**

**Hexahydroptalic Anhydride, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**MUGS**

**80350**

**Hexosaminidase A (MUGS), Serum**

**Clinical Information:** Tay-Sachs disease and Sandhoff disease are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and
hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs Disease: Tay-Sachs disease is caused by a deficiency of hexosaminidase A due to a defect in the alpha subunit. This autosomal recessive condition results from 2 mutations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency in hexosaminidase A; those with higher residual enzyme activity may have a milder clinical presentation with a later age of onset. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macroencephaly due to cerebral gliosis, and a characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between ages 2 and 10 with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of a pseudodeficiency allele. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel that includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. A very small group of patients affected with Tay-Sachs disease have the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant of hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Sandhoff Disease (not detected by MUGS): Sandhoff disease (deficiency of hexosaminidase A and B due to a defect in the beta subunit) is an autosomal recessive condition resulting from 2 mutations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Diagnostic and Carrier Testing: Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of
Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with a high percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Second-order test for diagnosing the B1 variant of Tay-Sachs disease. This test should be ordered when the patient exhibits symptoms of Tay-Sachs disease, but has tested as normal, indeterminate, or carrier by either NAGS / Hexosaminidase A and Total Hexosaminidase, Serum or NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes

**Interpretation:** Interpretation is provided with report. The B1 mutation results in depressed Hex A isoenzyme as assayed by MUGS using the natural substrate, 4-MUGS; whereas it reacts normally to the artificial substrate 4-MUG as assayed by NAGW, NAGR, and NAGS. Follow-up testing using leukocytes is recommended for indeterminate results.

**Reference Values:**
- 1.23-2.59 U/L (normal)
- 1.16-1.22 U/L (indeterminate)
- 0.58-1.15 U/L (carrier)

**Clinical References:**

**NAGW**

**Hexosaminidase A and Total Hexosaminidase, Leukocytes**

**Clinical Information:** Tay-Sachs disease and Sandhoff disease are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs Disease: Tay-Sachs disease is caused by a deficiency of hexosaminidase A due to a defect in the alpha subunit. This autosomal recessive condition results from 2 mutations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency in hexosaminidase A; those with higher residual enzyme activity may have a milder clinical presentation with a later age of onset. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macroencephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease is often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle...
wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of a pseudodeficiency allele. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff Disease: Sandhoff disease (deficiency of hexosaminidase A and B due to a defect in the beta subunit) is an autosomal recessive condition resulting from 2 mutations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Diagnostic and Carrier Testing: Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

Useful For: Carrier detection and diagnosis of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease (testing option-this is not the recommended test)

Interpretation: Interpretation is provided with report. Hexosaminidase A usually composes >62% of the total hexosaminidase activity in leukocytes (normal =63%-75% A). In leukocytes, the percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs disease: -63% to 75% hexosaminidase A is normal (noncarrier) -58% to 62% hexosaminidase A is indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for prenatal diagnosis if desired) -<58% hexosaminidase A is a carrier (molecular testing recommended to discern disease-causing mutations from pseudodeficiency alleles and to allow for prenatal diagnosis, if desired) -<20% hexosaminidase A is consistent with a diagnosis of Tay-Sachs disease In leukocytes, the total hexosaminidase in combination with the percent hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with Sandhoff disease: -> or =76% hexosaminidase A is suggestive of a Sandhoff carrier, when the total hexosaminidase is depressed -Total hexosaminidase
activity near zero with nearly 100% hexosaminidase A is consistent with Sandhoff disease

**Reference Values:**

**HEXOSAMINIDASE TOTAL**

- < or =15 years: > or =20 nmol/min/mg
- > or =16 years: 16.4-36.2 nmol/min/mg

**HEXOSAMINIDASE PERCENT A**

- < or =15 years: 20-80% of total
- > or =16 years: 63-75% of total

**Clinical References:**


**Hexosaminidase A and Total Hexosaminidase, Serum**

**Clinical Information:** Tay-Sachs disease and Sandhoff disease are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs Disease: Tay-Sachs disease is caused by a deficiency of hexosaminidase A due to a defect in the alpha subunit. This autosomal recessive condition results from 2 mutations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency in hexosaminidase A; those with higher residual enzyme activity may have a milder clinical presentation with a later age of onset. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macroencephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of a
pseudodeficiency allele. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff Disease: Sandhoff disease (deficiency of hexosaminidase A and B due to a defect in the beta subunit) is an autosomal recessive condition resulting from 2 mutations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Diagnostic and Carrier Testing: Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Carrier detection and diagnosis of Sandhoff disease (NAGS / Hexosaminidase A and Total Hexosaminidase, Serum is the recommended test) Carrier detection and diagnosis of Tay-Sachs disease (See also NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex and NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes for additional testing options).

**Interpretation:** Interpretation is provided with report.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Units</th>
<th>&lt; or =15 years</th>
<th>&gt; or =16 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEXOSAMINIDASE TOTAL, S</td>
<td>nmol/min/mL</td>
<td>&gt; or =20</td>
<td>10.4-23.8</td>
</tr>
<tr>
<td>HEXOSAMINIDASE PERCENT A, S</td>
<td>%</td>
<td>20-90%</td>
<td>56-80%</td>
</tr>
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</table>

Hexosaminidase A and Total, Leukocytes/Molecular Reflex

Clinical Information: Tay-Sachs disease and Sandhoff disease are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs Disease: Tay-Sachs disease is caused by a deficiency of hexosaminidase A due to a defect in the alpha subunit. This autosomal recessive condition results from 2 mutations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency in hexosaminidase A; those with higher residual enzyme activity may have a milder clinical presentation with a later age of onset. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macroencephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of a pseudodeficiency allele. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff Disease: Sandhoff disease (deficiency of hexosaminidase A and B due to a defect in the beta subunit) is an autosomal recessive condition resulting from 2 mutations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Diagnostic and Carrier Testing: Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum.
leukocytes, and cultured fibroblasts. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Carrier detection and diagnosis of Tay-Sachs disease (See also NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes and NAGS / Hexosaminidase A and Total Hexosaminidase, Serum for additional testing options). Recommended test for carrier detection of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease (testing option-not the recommended test)

**Interpretation:** Interpretation is provided with report. Hexosaminidase A usually composes >62% of the total hexosaminidase activity in leukocytes (normal = 63%-75% A). In leukocytes, the percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs disease: -63% to 75% hexosaminidase A is normal (noncarrier) -58% to 62% hexosaminidase A is indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for prenatal diagnosis if desired) <-58% hexosaminidase A is a carrier (molecular testing recommended to discern disease-causing mutations from pseudodeficiency alleles and to allow for prenatal diagnosis if desired) <-20% hexosaminidase A is consistent with a diagnosis of Tay-Sachs disease. In leukocytes, the total hexosaminidase in combination with the percent hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with Sandhoff disease: -> or =76% hexosaminidase A is suggestive of a Sandhoff carrier, when the total hexosaminidase is depressed -Total hexosaminidase activity near zero with nearly 100% hexosaminidase A is consistent with Sandhoff disease

**Reference Values:**

**HEXOSAMINIDASE TOTAL**

< or =15 years: > or =20 nmol/min/mg

> or =16 years: 16.4-36.2 nmol/min/mg

**HEXOSAMINIDASE PERCENT A**

< or =15 years: 20-80% of total

> or =16 years: 63-75% of total

Hickory Shagbark (Carya ovata) IgE

**Interpretation:**
- Class IgE (kU/L) Comment
  - 0 < 0.35 Below Detection
  - 0.35 - 0.69 Low Positive
  - 0.70 - 3.49 Moderate Positive
  - 3.50 - 17.49 Positive
  - 17.50 - 49.99 Strong Positive
  - 50.00 - 99.99 Very Strong Positive
  - > 99.99 Very Strong Positive

**Reference Values:**
- < 0.35 kU/L

Hippuric Acid, Urine

**Reference Values:**
- Reporting limit determined each analysis

Creatinine (mg/L):
- U.S. Population (10th – 90th percentiles, median)
  - All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
  - Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
  - Females: 273 - 2170 mg/L, median 994 (n=11,635)

Hippuric Acid (g/L)
- Synonym(s): Hippurate; n-Benzoylglycine
- Normal for unexposed populations is generally less than 1.6 g/L.

Hippuric Acid (Creatinine corrected) (g/g Creat)
- Synonym(s): Hippurate; n-Benzoylglycine
- Normal for unexposed populations is generally less than 1.5 g/g creatinine.

Specific Gravity Confirmation
- Physiologic range: 1.010 - 1.030

Histamine Plasma

**Reference Values:**
- < 1.0 ng/mL

Histamine, 24-Hour Urine

**Reference Values:**
- Histamine, 24 hr Urine: 0.006 – 0.131 mg/24 h

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>g/24 hours</th>
</tr>
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<tbody>
<tr>
<td>3-8</td>
<td>0.11 - 0.68</td>
</tr>
<tr>
<td>9-12</td>
<td>0.17 - 1.41</td>
</tr>
<tr>
<td>13-17</td>
<td>0.29 - 1.87</td>
</tr>
<tr>
<td>Adults</td>
<td>0.63 - 2.50</td>
</tr>
</tbody>
</table>
Histamine, Whole Blood

Reference Values:
180 - 1800 nmol/L

Histone Autoantibodies, Serum

Clinical Information: Histones are the most basic protein components of chromatin and their structures are highly conserved in different species. Five classes of histones called H1, H2, H2b, H3, and H4 have been described and are characterized by their molecular weights, ranging from 11 to 23 kilodalton (kD), and their content of the basic amino acids lysine and arginine. Histone autoantibodies may react with any of the 5 classes of histones.(1,2) Autoantibodies to total histones are elicited by unknown mechanisms in patients treated with certain drugs, particularly procainamide, hydralazine, quinidine, alpha methylidopa, penicillamine, and isoniazid. Those patients may have signs and symptoms that resemble systemic lupus erythematosus (SLE). This disorder is identified as drug-induced lupus. Testing for autoantibodies to total histones is useful for evaluating patients suspected of having drug-induced lupus. Such patients will usually have a positive test for histone autoantibodies and a negative test for autoantibodies to double stranded DNA (dsDNA). Patients with SLE have positive tests for both types of autoantibodies.

Useful For: Evaluating patients suspected of having drug-induced lupus

Interpretation: A positive result for histone autoantibodies with a negative result for autoantibodies to double-stranded DNA (anti-ds-DNA) is consistent with drug-induced lupus. A positive result for histone autoantibodies with a positive result for anti-dsDNA autoantibodies is consistent with systemic lupus erythematosus.

Reference Values:
<1.0 Units (negative)
1.0-1.5 Units (borderline)
>1.5 Units (positive)
Units are arbitrarily based on positive control serum.
Reference values apply to all ages.


Histoplasma Antibody, Serum

Clinical Information: Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and in immunosuppressed patients.

Useful For: Aiding in the diagnosis of active histoplasmosis

Interpretation: Complement fixation (CF) titers > or =1:32 indicate active disease. A rising CF titer is associated with progressive infection. Positive immunodiffusion test results supplement findings of the CF test. The simultaneous appearance of both H and M precipitin bands indicates active histoplasmosis. The M precipitin band alone indicates early or chronic disease or a recent histoplasmosis skin test. Patients infected with Histoplasma capsulatum demonstrate a serum antibody with a rising titer within 6 weeks of infection. A rising titer is associated with progressive infection. Specific antibody persists for a few weeks to a year, regardless of clinical improvement.

Reference Values:
Mycelial by CF: negative (positives reported as titer)
Histoplasma Antibody, Spinal Fluid

**Clinical Information:** Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and immunosuppressed patients.

**Useful For:** Aiding in the diagnosis of Histoplasma meningitis

**Interpretation:** Any positive serologic result in spinal fluid is significant. Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis.

**Reference Values:**
- Mycelial by CF: negative (positives reported as titer)
- Yeast by CF: negative (positives reported as titer)
- Antibody by immunodiffusion: negative (positives reported as band present)


Histoplasma Antigen, Urine

**Clinical Information:** Histoplasma capsulatum is a dimorphic fungus endemic to the Midwest United States, particularly along the Mississippi River and Ohio River valleys. Infection occurs following inhalation of fungal microconidia and subsequent clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient’s underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk for severe infection include those with impaired cellular immunity, patients who have undergone organ transplantation, are HIV positive, or have a hematologic malignancy. The available laboratory methods for the diagnosis of Histoplasma capsulatum infection include fungal culture, molecular techniques, serologic testing, and antigen detection. Among these, while culture remains the gold standard diagnostic test and is highly specific, prolonged incubation is often required and sensitivity decreases (9%-34%) in cases of acute or localized disease. Similarly, molecular methods offer high specificity, but decreased sensitivity. Serologic testing likewise offers high specificity, however results may be falsely negative in immunosuppressed patients or those who present with acute disease. Also, antibodies may persist for years following disease resolution, thereby limiting the clinical specificity. Detection of Histoplasma capsulatum antigen from urine samples has improved sensitivity (80%-95%) for the diagnosis of active histoplasmosis compared to both culture and serology. Additionally, urine antigen levels can be followed to monitor patient response to therapy, with declining levels consistent with disease resolution. Notably, however, Histoplasma capsulatum antigen may persist at low levels following completion of antifungal therapy and clinical improvement.

**Useful For:** Aids in the diagnosis of Histoplasma capsulatum infection Monitoring Histoplasma antigen titers in urine

**Interpretation:** Presence of Histoplasma antigen in urine is indicative of current or recent infection with Histoplasma capsulatum. Declining levels of Histoplasma antigen are indicative of disease regression and can be used to monitor patient response to antifungal therapy. Notably, low-level titers may persist for extended periods of time following appropriate treatment and resolution of infection. Urine samples with "Indeterminate” results are automatically reflexed to MiraVista Diagnostics (Indianapolis, IN) for
confirmatory testing. Clinical decisions regarding Histoplasma infection should not be based on an Indeterminate result alone. Other laboratory findings, including Histoplasma serology, fungal culture, and molecular tests (eg, RT-PCR) should be considered, alongside clinical presentation and exposure history, to confirm the diagnosis. The absence of detectable Histoplasma antigen in urine is consistent with the absence of infection. Repeat testing on a fresh urine sample if early acute Histoplasma infection is suspected.

Reference Values:

Histoplasma Ag Result
Negative

Histoplasma Ag Value
Negative: 0.00 - 0.10
Indeterminate: 0.11-0.49
Positive: > or =0.50


Histoplasma capsulatum/Blastomyces dermatitidis, Molecular Detection, PCR

Clinical Information: Infections with Blastomyces dermatitidis and Histoplasma capsulatum cause a variety of clinical manifestations ranging from self-limited, mild pulmonary illness to potentially life-threatening, disseminated disease. Patients at risk for disseminated disease include neonates and immunosuppressed individuals, particularly those with AIDS, hematologic malignancies, or a recent transplant. Primary infections are acquired through inhalation of microconidia that are present in the environment. In the United States, most cases of blastomycosis and histoplasmosis occur along the Ohio and Mississippi River valleys. The gold standard for diagnosis of blastomycosis and histoplasmosis remains isolation of the organisms in culture. Although sensitive, recovery in culture and subsequent identification may require days to weeks. The organisms can be identified after growth in culture using traditional macro- and microscopic morphologic techniques or through the use of nucleic acid hybridization probes. Hybridization probe-based procedures are rapid and demonstrate good sensitivity and specificity from culture, although some cross-reactivity with relatively uncommon fungal organisms has been reported. Additional diagnostic tests that can be utilized for these organisms include stains, histopathology, serology, and antigen detection with each of these methods offering advantages and limitations depending on the stage of the illness and the status of the patient. Fungal stains (eg, calcofluor white) offer a rapid diagnostic approach, but demonstrate poor sensitivity and specificity. Serologic tests such as complement fixation and immunodiffusion are noninvasive, but are laborious, subjective, and may show low sensitivity, especially in immunocompromised hosts. Antigen detection also offers a noninvasive approach, but has been demonstrated to show cross-reactivity with antigens from closely related fungal species. Molecular techniques have been established as sensitive and specific methods for the diagnosis of infectious diseases and have the added advantage of a rapid turnaround time for results. Due to the limitations of conventional diagnostic methods for blastomycosis and histoplasmosis, a single tube, real-time PCR assay was developed and verified for the detection and differentiation of Blastomyces dermatitidis and Histoplasma capsulatum directly from clinical specimens.

Useful For: Rapid detection of Histoplasma capsulatum and Blastomyces dermatitidis DNA An aid in the rapid diagnosis of histoplasmosis and blastomycosis

Interpretation: A positive result for Histoplasma capsulatum indicates presence of Histoplasma DNA; a positive result for Blastomyces dermatitidis indicates presence of Blastomyces DNA. A negative result indicates absence of detectable Histoplasma capsulatum and Blastomyces dermatitidis DNA. Fungal culture has increased sensitivity over this PCR assay and should always be performed when the PCR is
negative.

**Reference Values:**
Not applicable

**Clinical References:**

**Histoplasma capsulatum/Blastomyces dermatitidis, Molecular Detection, PCR, Blood**

**Clinical Information:** Infections with Blastomyces dermatitidis and Histoplasma capsulatum cause a variety of clinical manifestations ranging from self-limited, mild pulmonary illness to potentially life-threatening, disseminated disease. Patients at risk for disseminated disease include neonates and immunosuppressed individuals, particularly those with AIDS, hematologic malignancies, or a recent transplant. Primary infections are acquired through inhalation of microconidia that are present in the environment. In the United States, most cases of blastomycosis and histoplasmosis occur along the Ohio and Mississippi River valleys. The gold standard for diagnosis of blastomycosis and histoplasmosis remains isolation of the organisms in culture. Although sensitive, recovery in culture and subsequent identification may require days to weeks. The organisms can be identified after growth in culture using traditional macro- and microscopic morphologic techniques or through the use of nucleic acid hybridization probes. Hybridization probe-based procedures are rapid and demonstrate good sensitivity and specificity from culture, although some cross-reactivity with relatively uncommon fungal organisms has been reported. Additional diagnostic tests that can be utilized for these organisms include stains, histopathology, serology, and antigen detection with each of these methods offering advantages and limitations depending on the stage of the illness and the status of the patient. Fungal stains (eg, calcofluor white) offer a rapid diagnostic approach, but demonstrate poor sensitivity and specificity. Serologic tests such as complement fixation and immunodiffusion are noninvasive, but are laborious, subjective, and may show low sensitivity, especially in immunocompromised hosts. Antigen detection also offers a noninvasive approach, but has been demonstrated to show cross-reactivity with antigens from closely related fungal species. Molecular techniques have been established as sensitive and specific methods for the diagnosis of infectious diseases and have the added advantage of a rapid turnaround time for results. Due to the limitations of conventional diagnostic methods for blastomycosis and histoplasmosis, a single tube, real-time PCR assay was developed and verified for the detection and differentiation of Blastomyces dermatitidis and Histoplasma capsulatum directly from clinical specimens.

**Useful For:** Rapid detection of Histoplasma capsulatum and Blastomyces dermatitidis DNA

**Interpretation:** A positive result for Histoplasma capsulatum indicates presence of Histoplasma DNA; a positive result for Blastomyces dermatitidis indicates presence of Blastomyces DNA. A negative result indicates absence of detectable Histoplasma capsulatum and Blastomyces dermatitidis DNA.

**Reference Values:**
Not applicable

**Clinical References:**
Histoplasma/Blastomyces Antibody Panel, Spinal Fluid

Clinical Information: Histoplasma: Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and immunosuppressed patients. Blastomyces: The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

Useful For: Histoplasma: Aiding in the diagnosis of Histoplasma meningitis Blastomyces: Detection of antibodies in patients having blastomycosis

Interpretation: Histoplasma: Any positive serologic result in spinal fluid is significant. Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis. Blastomyces: A positive result indicates that IgG and/or IgM antibodies to Blastomyces were detected. The presence of antibodies is presumptive evidence that the patient was or is currently infected with (or exposed to) Blastomyces. A negative result indicates that antibodies to Blastomyces were not detected, but does not rule out infection. All specimens testing equivocal will be repeated. Specimens testing equivocal after repeat testing should be submitted for further testing by another conventional serologic test (eg, CBL / Blastomyces Antibody by Immunodiffusion, Spinal Fluid).

Reference Values:
HISTOPLASMA ANTIBODY, SPINAL FLUID
Mycelial by complement fixation: Negative
Yeast by complement fixation: Negative
Antibody by immunodiffusion: Negative

BLASTOMYCES ANTIBODY BY EIA, SPINAL FLUID
Negative


HIV-1 and HIV-2 Antibodies for Cadaveric or Hemolyzed Specimens, Serum

Clinical Information: Epidemiological data indicate that AIDS is caused by at least 2 types of HIV. The first virus, HIV-1, has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. They may fall into undetectable levels in the terminal stage of AIDS. See HIV Testing Algorithm (Fourth Generation Screening Assay) Including Follow-up of Reactive HIV Rapid Serologic Test Results in Special Instructions.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HIV infection (assay kit is FDA-approved for
Interpretation: A reactive HIV-1/-2 antibody screen result obtained by EIA suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Confirmatory testing by HIV-1/-2 antibody differentiation or HIV-1 specific Western blot (WB) assay is necessary to verify the presence of HIV-1 infection. The presence of HIV-2 infection is screened by HIV-2 antibody-specific EIA with confirmation by HIV-2 antibody-specific immunoblot assay. All EIA-reactive specimens tested will automatically be tested by HIVDI / HIV-1 and HIV-2 Antibody Differentiation, Serum at an additional charge. Please see the individual unit code for interpretation of these subsequent test results. All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/-2 antibody EIA screen result indicates the absence of HIV-1 or HIV-2 infection. However, for specimens that are reactive by the rapid HIV antibody tests, confirmatory testing by HV1WB / HIV-1 Antibody Confirmation by Western Blot, Serum is recommended even if the EIA results are negative.

Reference Values:
Negative
See HIV Serologic Interpretive Guide in Special Instructions for further interpretive information.

Clinical References:
1. Constantine N: HIV antibody assays May 2006. In HIV InSite Knowledge Base (online textbook). Available at: http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-02-02-01

HIVDI
62421

HIV-1 and HIV-2 Antibody Confirmation and Differentiation, Serum

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient’s immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers’ instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in serum specimens that show reactive results with third- (HIV-1/-2 antibody only) and fourth- (HIV antigen and antibody) generation HIV serologic assays

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. If acute or early HIV infection is suspected, detection of HIV-1 RNA (HIVDQ / HIV-1 RNA Detection and Quantification, Plasma) and/or HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended, based on patientâ€™s clinical and epidemiologic exposure history. Positive HIV-1 antibody, but negative HIV-2 antibody results, indicates the presence of HIV-1 infection. Together
with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIV-1 RNA (HIVDQ) is recommended to verify and confirm the diagnosis of HIV-1 infection prior to initiating antiretroviral treatment. Positive HIV-1 antibody, but indeterminate HIV-2 antibody results, indicates the presence of HIV-1 infection, with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Submit a plasma specimen for detection of HIV-1 RNA (HIVDQ). However, such result patterns may rarely indicate early HIV-2 infection (ie, HIV-2 coinfection) in HIV-1-infected individuals. For individuals at risk for HIV-2 infection (based on epidemiologic exposure history), a plasma specimen should be submitted also for HIV-2 DNA/RNA (FHV2Q). Indeterminate HIV-1 antibody, but negative HIV-2 antibody results, suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. If patient has known risk factors for HIV-1 infection, a new specimen should be submitted for HIV-2 serologic testing (HIV2 / HIV-2 Antibody Evaluation, Serum or HIV2M / HIV-2 Antibody Screen, Serum) or HIV-2 DNA/RNA (FHV2Q). Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, suggests either very early HIV-2 infection (in individuals with risk factors) or presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. If patient has known risk factors for HIV-2 infection (based on patient's clinical and epidemiologic history), a new specimen should be submitted for HIV-2 serologic testing (HIV2 or HIV2M) or HIV-2 DNA/RNA (FHV2Q). Positive results for both HIV-1 and HIV-2 antibodies suggest probable the presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to: a) HIV-1 infection with HIV-2 antibody cross-reactivity; or b) HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. Based on patient's clinical and epidemiologic history, plasma specimens should be submitted for detection of HIV-1 RNA (HIVDQ) and/or HIV-2 DNA/RNA (FHV2Q). Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). For individuals at risk for HIV infection, plasma specimens should be submitted for detection of HIV-1 RNA (HIVDQ) and/or HIV-2 DNA/RNA (FHV2Q), depending on the epidemiologic exposure history. Negative HIV-1 antibody, but positive HIV-2 antibody results, indicates the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted plasma specimen for HIV-2 DNA/RNA (FHV2Q) is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody, but positive HIV-2 antibody results, usually indicates the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a new specimen for HIV-2 serologic testing (HIV2 or HIV2M) or a plasma specimen for HIV-2 DNA/RNA (FHV2Q). If the patient is at risk for HIV-1 infection (based on patient's clinical and epidemiologic history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIVDQ). Indeterminate HIV-1 antibody, but positive HIV-2 antibody results, indicates the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for (FHV2Q). However, such result patterns may rarely indicate early HIV-1 infection (ie, HIV-1 coinfection) in HIV-2-infected individuals. For individuals at risk for HIV-1 infection, (based on epidemiologic exposure history), plasma specimen should be submitted also for detection of HIV-1 RNA (HIVDQ). See HIV Testing Algorithm (Fourth Generation Screening Assay) Including Follow-up of Reactive HIV Rapid Serologic Test Results in Special Instructions.

Reference Values:

See HIV Serologic Interpretive Guide in Special Instructions for further interpretive information.

HV1CM 60357

HIV-1 and HIV-2 Antibody Screen for Hemolyzed Specimens, Serum

Clinical Information: Epidemiological data indicate that AIDS is caused by at least 2 types of HIV. The first virus, HIV-1, has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. They may fall into undetectable levels in the terminal stage of AIDS. See HIV Testing Algorithm (Fourth Generation Screening Assay) Including Follow-up of Reactive HIV Rapid Serologic Test Results in Special Instructions.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in cadaveric or hemolyzed serum specimens from asymptomatic patients with or without risk factors for HIV infection (assay kit is FDA-approved for testing cadaveric or hemolyzed blood specimens)

Interpretation: A reactive HIV-1/-2 antibody screen result obtained by EIA suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Confirmatory testing by HIV-1/-2 antibody differentiation or HIV-1 specific Western blot (WB) assay is necessary to verify the presence of HIV-1 infection. The presence of HIV-2 infection is screened by HIV-2 antibody-specific EIA with confirmation by HIV-2 antibody-specific immunoblot assay. All EIA-reactive specimens tested will automatically be tested by HIVDI / HIV-1 and HIV-2 Antibody Differentiation, Serum at an additional charge. Please see the individual unit code for interpretation of these subsequent test results. All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/-2 antibody EIA screen result indicates the absence of HIV-1 or HIV-2 infection. However, for specimens that are reactive by the rapid HIV antibody tests, confirmatory testing by HV1WB / HIV-1 Antibody Confirmation by Western Blot, Serum is recommended even if the EIA results are negative.

Reference Values:
Negative

See HIV Serologic Interpretive Guide in Special Instructions for further interpretive information.

HIV-1 and HIV-2 Antigen and Antibody Evaluation, Serum

**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Screening for HIV-1 and/or HIV-2 infection in asymptomatic patients Diagnosis of HIV-1 and/or HIV-2 infection in symptomatic patients Follow-up testing of individuals with reactive results from rapid HIV tests

**Interpretation:** Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule out acute HIV infection. If acute HIV-1 infection is suspected, detection of HIV RNA (HIVDQ / HIV-1 RNA Detection and Quantification, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. Reactive result of this assay does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV-1/-2 antibody differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge), HIV-1 antibody confirmation by Western blot, and HIV-2 antibody confirmation. See these individual tests for interpretation of their results. All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second serum specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. See HIV Testing Algorithm (Fourth Generation Screening Assay) Including Follow-up of Reactive HIV Rapid Serologic Test Results in Special Instructions.

**Reference Values:**

**Clinical References:**

HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma

**Clinical Information:** Human immunodeficiency virus (HIV)-1 infection is usually confirmed by detection of HIV-1-specific antibodies in serum. However, serologic testing may not reliably identify
HIV-1 infection in neonates with passively acquired maternal HIV-1 antibodies or with incompletely developed immune systems, individuals with early HIV-1 infection (<30 days from infection), or individuals with "indeterminate" HIV-1 antibody results by supplemental serologic assays. In these situations, detection of HIV-1 nucleic acids (RNA or proviral DNA) by PCR can provide definitive, early evidence of HIV-1 infection (approximately 10 to 14 days after infection), when results of routine diagnostic assays may be inconclusive. Upon entry into human cells (including peripheral blood mononuclear cells), the HIV-1 RNA is converted into complementary DNA (cDNA) by reverse transcription. These linear cDNA strands are then integrated into the host cell genome, thus representing the proviral form of HIV-1. mRNA, transcribed from the proviral DNA, is used to synthesize the proteins required to make new viral particles. These proteins and viral RNA are packaged in the host's cytoplasm and released from the cell, completing the life cycle of the virus. HIV-1 DNA and/or RNA tests are recommended at 14 to 21 days, 1 to 2 months, and 4 to 6 months after birth, in infants born to HIV-1-infected mothers. Breastfeeding infants should be tested at baseline (1 to 2 days), 4 to 6 weeks, 3 months, and 4 to 6 months after birth. Two consecutive positive HIV-1 virologic test results (HIV-1 DNA and/or RNA) are necessary for confirming the diagnosis of HIV-1 infection in infants <18 months of age.

**Useful For:**
- Virologic detection of HIV-1 infection in infants <18 months of age (an age group for which serologic tests are unreliable) born to HIV-1-infected mothers
- Early detection of acute HIV-1 infection in children and adults who may be receiving combination antiretroviral prophylaxis or pre-emptive treatment
- Determining eradication of HIV-1 in individuals receiving combination highly active antiretroviral therapies

**Interpretation:** A "Detected" result is consistent with HIV infection (see Cautions section). Per CDC and USPHS recommendations, a second specimen should be collected from any patient with first-time detectable HIV-1 DNA or RNA result and tested to verify the diagnosis of HIV-1 infection. An "Undetected" result indicates that neither HIV-1 DNA nor RNA is detected in the specimen (see Cautions). Repeat testing in 1 to 2 months is recommended for those at risk of HIV-1 infection. The lower limits of detection (based on 95% detection rate) of this assay in plasma are 311 copies/mL for HIV-1 DNA and 75 copies/mL for HIV-1 RNA. An "Inconclusive" result indicates that the absence or presence of HIV-1 DNA or RNA could not be determined with certainty after repeat testing of the clinical specimens in the laboratory, possibly due to PCR inhibition. Submission of a new specimen for testing is recommended.

**Reference Values:**

**Clinical References:**
HIV viral load, thereby improving patient outcome. HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA (cDNA) by the action of the viral reverse transcriptase (RT) gene product. RT has little proofreading capacity and, therefore, incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease catalyzes a polyprotein to produce peptides necessary for active viral replication. Although HAART (combination of nucleoside analog, nonnucleoside agent and/or protease inhibitor) may be effective in reducing the viral load, genotypic mutations arising in the drug-targeted HIV gene loci due to selective pressure from antiviral therapy result in antiviral resistance that may compromise such therapy. Amplification and analysis of drug-targeted HIV-gene sequence allows identification of changes in nucleotide bases and associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are deemed as mutations by comparing the sequence data of the patient’s HIV strain to those of a wild-type HIV strain. The significance of these genotypic mutations in relation to antiviral resistance is then determined by a set of interpretive rules developed by a consensus panel of leading experts in the field of HIV resistance. Relevant data presented at a recognized scientific conference or published in peer-reviewed journals are considered by the consensus panel in developing these rules. When necessary, reliable unpublished drug resistance data known to consensus panel members may be considered in the process. The interpretive rules are updated by the consensus panel annually after reviewing newly published data on HIV-1 genotypic drug resistance mutations.

**Useful For:** Identification of HIV-1 genotypic mutations associated with resistance to nucleotide reverse-transcriptase inhibitors, non-nucleotide reverse-transcriptase inhibitors, and protease inhibitors

**Guiding initiation or change of drug combinations for the treatment of HIV-1 infection**

**Interpretation:** Detectable HIV-1 genotypic mutations conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, M184V) resulting from the mutations. Susceptible (Susc) indicates that the genotypic mutations present in patient’s HIV-1 strain have not been associated with resistance to the specific drug in question. Resistant (Resist) indicates that genotypic detected have been associated with maximum reduction in susceptibility to the specific drug. Possible Resistance (PR) indicates that genotypic mutations detected have been associated with 1 or both of the following outcomes: -Diminished virologic response in some, but not all, patients having virus with these mutations; -Intermediate decrease in susceptibility of the virus to the specific drug. Unable to genotype indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient’s HIV strain. Probable cause of such poor sequence data is polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction. Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of either low HIV-1 viral load (ie, <500 copies/mL) or ambiguous or incomplete viral target sequences generated from the assay.

**Reference Values:**

Not applicable

**Clinical References:***

   https://www.iasusa.org/content/antiretroviral-drug-resistance-testing-adult-hiv-1-infection
   https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-2014-recommendations-international-antiviral-society-usa-panel
   https://www.iasusa.org/sites/default/files/tam/22-3-642.pdf
patients receiving raltegravir in a clinical trial experienced virologic failure at 48 weeks and genotypic analysis detected raltegravir associated resistance mutations in 68% of virologic failures. This assay amplifies and sequences the HIV-1 integrase gene and reports mutations at positions associated with integrase inhibitor drug resistance.

**Interpretation:** The method used in this test is RT-PCR and sequencing of the HIV-1 integrase gene. The phrases "resistance predicted" and "probable or emerging resistance" refer to the application of the interpretive rules. The FDA has not reviewed all of the interpretive rules used by the laboratory to predict drug resistance. FDA may not currently recognize some of the HIV gene mutations reported as predictive of drug resistance, but the laboratory considers these mutations to be associated with resistance to anti-viral drugs based on current clinical or scientific studies.

**Reference Values:**
Reference Range(s): See Lab Report

### HIV-1 RNA Detection and Quantification, Plasma

**Clinical Information:** Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for >99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 18 months of age, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the United States Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends use of proviral DNA or RNA tests for the detection of HIV infection in infants born to HIV-infected mothers.(1)

**Useful For:** Diagnosis of HIV-1 infection in individuals with acute or early HIV-1 infection Diagnosis of HIV-1 infection in infants of <18 months of age born to HIV-1-infected mothers Quantifying plasma HIV-1 RNA levels (viral load) in HIV-1-infected individuals: -Before initiating anti-HIV-1 drug therapy (baseline viral load) -Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy -Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression while on or off antiretroviral drug therapy

**Interpretation:** This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load <20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, less than 3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ”>10,000,000 copies/mL” with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level” indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patientäó»s response to antiretroviral therapy, the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of >200 copies/mL, which eliminates most cases of viremia resulting from isolated
blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

Reference Values:
Undetected

Clinical References:

HIV-1 RNA Quantification with Reflex to HIV-1 Genotypic Drug Resistance, Plasma

Clinical Information:
HIV-1 is an RNA virus that infects human host cells and is then converted to complementary DNA (cDNA) by the action of viral reverse transcriptase. HIV-1 is the causative agent of AIDS, a severe, life-threatening condition. Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for >99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. Studies have identified a number of mutations associated with antiviral resistance. Genotypic analysis allows identification of nucleotide changes associated with HIV drug resistance. When combination therapy fails, genotyping for drug resistance mutations may help direct appropriate changes in antiretroviral therapy and may result in at least a short-term benefit, as evidenced by viral load reduction.

Useful For:
Detecting and quantifying plasma HIV-1 RNA levels (viral load) in HIV-1-infected patients, followed by genotypic determination of viral resistance to anti-HIV drugs Guiding initiation or change of antiretroviral treatment regimens

Interpretation:
HIV-1 detection and quantification: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA within the plasma specimen. A result of "<20 IU/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load <20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that
HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of >200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-to-drug interactions, and patient adherence. If the viral load is > or =500 copies/mL, genotypic anti-HIV-1 drug resistance mutation analysis is performed automatically at an additional charge. Sequence data of the patient's viral strain is compared with those in a database of known drug resistance mutations. Results are provided that highlight those codon changes associated with specific drug resistance. These mutations are categorized and reported. HIV-1 genotypic drug resistance analysis: "Susceptible" indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug in question. "Resistant" indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug. "Possible resistance" indicates that genotypic mutations detected have been associated with 1 or both of the following outcomes: -Diminished virologic response in some, but not all, patients having virus with these mutations -Intermediate decrease in susceptibility of the virus to the specific drug. "Unable to genotype" indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient's HIV strain. Possible causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction. "Inconclusive" indicates inability of the assay to reliably determine antiviral resistance because of either low HIV-1 viral load (ie, <500 copies/mL) or ambiguous or incomplete viral target sequences generated from the assay.

Reference Values:
Undetected

Clinical References:

HIV-2 Antibody Confirmation, Serum

Clinical Information: Human immunodeficiency virus type 2 (HIV-2) is a lentivirus, a retrovirus in the same genus (Lentiviridae) as HIV-1. It was first isolated in 1986 in West Africa, where it is currently endemic. As of June 2010, CDC has reported a total of 166 cases that met the CDC case definition of HIV-2 infection in the United States. Most of these cases were found in the northeastern United States, and the majority had a West African origin or connection. Compared to HIV-1 infection, HIV-2 infection is associated with slower rate of progression, low viral load (which may not be reliably measurable with current methods), slower rates of decline in CD4 cell count, and lower rates of transmission (sexually or vertically). Up to 95% of HIV-2-infected individuals are long-term nonprogressors, and individuals with undetectable HIV-2 viral load have similar survival rates as that of the uninfected population. However, HIV-2 does cause immunosuppression as well as AIDS with the same signs, symptoms, and opportunistic infections seen in HIV-1. Due to the rarity of HIV-2, there are scant data from controlled trials to inform management decisions. Although there are several FDA-approved screening assays to detect both combined HIV-1 and HIV-2 antibodies or HIV-2 antibodies alone, currently there is only 1 FDA-approved supplemental (confirmatory) HIV-2 serologic assay for clinical use in the United States. Interpretation of visible band patterns is complicated due to the significant cross-reactivity between HIV-1 and HIV-2 antibodies in this assay.

Useful For: Confirmation of the presence of HIV-2 antibodies in patients with repeatedly reactive
combined HIV-1 and HIV-2 antibody or HIV-2 antibody-only screening test results

**Interpretation:** Negative results for HIV-2 antibodies usually indicate absence of HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV-2 infection. If acute or early HIV-2 infection is suspected, detection of HIV-2 DNA/RNA RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended, based on patient's™ clinical and epidemiologic exposure history. Positive HIV-2 antibody results indicate the presence of HIV-2 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for HIV-2 DNA/RNA (FHV2Q). Indeterminate results HIV-2 antibodies indicate either very early HIV-2 infection (in individuals with risk factors) or presence of nonspecific cross-reactivity between the patient's™ specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). For individuals at risk for HIV-2 infection, plasma specimens should be submitted for detection of HIV-2 DNA/RNA (FHV2Q), depending on the epidemiologic exposure history.

**Reference Values:**
Negative
This confirmatory assay should be ordered only on specimens that are reactive by an HIV-2 antibody screening immunoassay.

**Clinical References:**
automatically confirmed by an HIV-2 antibody immunoblot assay with an additional charge. HIV-2 antibody immunoblot results are reported as either Positive, Negative, or Indeterminate. Negative screen results indicate the absence of HIV-2 antibodies. These results should be interpreted with caution in patients who are at high risk or have symptoms or signs of HIV infection.

**Reference Values:**
Negative

See HIV Serologic Interpretive Guide in Special Instructions for further interpretive information.

**Clinical References:**
1. Constantine N: HIV antibody assays May 2006. In HIV InSite Knowledge Base (online textbook). Available at: http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-02-02-01

**HIV-2 Antibody Screen, Serum**

**Clinical Information:** Epidemiologic data suggest that AIDS is caused by at least 2 types of HIV, HIV-1 and HIV-2. HIV-1 has been isolated from patients with AIDS and asymptomatic infected individuals. The closely related HIV-2 was first isolated from patients in West Africa in 1986, and the first case of AIDS due to HIV-2 in a patient was reported in the United States in 1988. HIV-2 appears to be endemic only in West Africa, but HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that region. HIV-2 infection is rare in the United States (<100 cases reported to date); most of the reported cases are from the northeastern states and involve persons from West Africa. Both HIV-1 and HIV-2 are transmitted by sexual contact, sharing contaminated needles, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. During the course of HIV-2 infection, antibodies are formed against the viral proteins p26 and gp34. Immunosuppressed patients may fail to develop these antibodies. At-risk patients with positive results for HIV-1/-2 antigen and antibody combination assays and/or indeterminate or negative results on HIV-1 antibody by Western blot (especially those showing reactivity only with HIV-1 core [p18, p24, or p55] and polymerase [p31, p51, or p66] proteins) should be investigated for the presence of HIV-2 antibodies.

**Useful For:** Screening for and detection of HIV-2 antibodies in asymptomatic individuals

**Interpretation:** Reactive screening test results suggest the presence of HIV-2 antibodies. All repeatedly reactive serum specimens are automatically confirmed by an HIV-2 antibody immunoblot assay with an additional charge. HIV-2 antibody immunoblot results are reported as Positive, Negative, or Indeterminate. Negative screen results indicate the absence of HIV-2 antibodies. These results should be interpreted with caution in patients who are at high risk or have symptoms or signs of HIV infection.

**Reference Values:**
Negative

See HIV Serologic Interpretive Guide in Special Instructions for further interpretive information.

**Clinical References:**
1. Constantine N: HIV antibody assays May 2006. In HIV InSite Knowledge Base (online textbook). Available at: http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-02-02-01
HIV-2 DNA/RNA Qualitative Real-Time PCR

Reference Values:
Reference Range: Not Detected

HLA A High Resolution

Reference Values:
A final report will be faxed under separate cover.

HLA B High Resolution

Reference Values:
A final report will be faxed under separate cover.

HLA C High Resolution

Reference Values:
A final report will be faxed under separate cover.

HLA Class I Molecular Typing Disease Association

Clinical Information: Human leukocyte antigens (HLA) are regulators of the immune response that play a key role in transplantation. HLA class I typing is most frequently applicable to organ transplant donor/recipient matching, provision of HLA-matched platelets for alloimmunized refractory patients, and for a small number of disease associations. Class I HLA antigens include A, B, and C loci. This assay is designed to provide low-to-medium resolution for HLA class I typing (A, B, C). Low-to-medium resolution defines the typing at the antigen level. This is in contrast to high-resolution typing, which defines typing at the allele (molecular) level and is used primarily for typing donor/recipient pairs for unrelated bone marrow transplantation.

Useful For: Determining class I HLA antigens on specimens for transplant candidates and their donors or those who have become refractory to platelet transfusions

Interpretation: Interpretation depends on the rationale for ordering the test. Assessments of acceptable donor/recipient matches are made on a case-by-case basis.

Reference Values:
Not applicable


HLA Class II Molecular Typing Disease Association

Clinical Information: Human leukocyte antigens (HLA) are regulators of the immune response that play a key role in transplantation. Sequence-specific oligonucleotides are designed to provide low-to-medium resolution for HLA Class II (DR and DQ) typing. Low-to-medium resolution defines the typing at the antigen level. This is in contrast to high-resolution typing, which defines typing at the allele (molecular) level and is used primarily for typing donor-recipient pairs for unrelated bone marrow transplantation.
**Useful For:** Determining HLA Class II compatibility on specimens from bone marrow and solid organ transplant candidates and their donors

**Interpretation:** Interpretation depends on the rationale for ordering the test. Assessments of acceptable donor/recipient matches are made on a case-by-case basis.

**Reference Values:**
Not applicable

**Clinical References:**

**HLA-B 5701 Genotype, Abacavir Hypersensitivity, Blood**

**Clinical Information:** The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*57:01 allele. Frequency of the HLA-B*57:01 allele varies with ethnicity, with a frequency of 6% to 7% in European populations, and up to 20% in Southwest Asian populations. The HLA-B*57:01 allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the HLA-B*57:01 allele are at an increased risk for abacavir hypersensitivity and it is not recommended for use in treating these individuals. Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the HLA-B*57:01 genotype and excluding HLA-B*57:01-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions.

**Useful For:** Identifying individuals with an increased risk of hypersensitivity reactions to abacavir, based on the presence of the human leukocyte antigen HLA-B*57:01 allele

**Interpretation:** Positivity for human leukocyte antigen allele HLA-B*57:01 confers high risk for hypersensitivity to abacavir. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
HLA-B 5701 Genotype, Abacavir Hypersensitivity, Saliva

Clinical Information: The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class 1 HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*57:01 allele. Frequency of the HLA-B*57:01 allele varies with ethnicity, with a frequency of 6% to 7% in European populations, and up to 20% in Southwest Asian populations. The HLA-B*57:01 allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the HLA-B*57:01 allele are at an increased risk for abacavir hypersensitivity and it is not recommended for use in treating these individuals. Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the HLA-B*57:01 genotype and excluding HLA-B*57:01-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions.

Useful For: Identifying individuals with an increased risk of hypersensitivity reactions to abacavir, based on the presence of the HLA-B*57:01 allele. Genotyping patients who prefer not to have venipuncture done.

Interpretation: Positivity for human leukocyte antigen allele HLA-B*57:01 confers high risk for hypersensitivity to abacavir. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values: An interpretive report will be provided.


HLA-B*5801 Genotype, Allopurinol Hypersensitivity, Blood

Clinical Information: The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class 1 HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*58:01 allele. Frequency of the HLA-B*58:01 allele varies with ethnicity, with a frequency of 6% to 7% in Asian populations, and 1% in Caucasian populations. Allopurinol is a drug widely used for hyperuricemia-related diseases such as gout, Lesch-Nyhan syndrome, and recurrent urate kidney stones.
However, this drug is one of the most common causes of severe cutaneous adverse reactions (SCAR), an umbrella term encompassing drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These reactions have a reported mortality rate of 20% to 25%. For individuals taking allopurinol, the presence of the HLA-B*58:01 allele has been strongly associated with allopurinol-induced SCAR. Guidelines from the Clinical Pharmacogenomics Implementation Consortium (CPIC) recommend HLA-B*58:01 genotyping be performed when considering prescribing allopurinol, and that allopurinol should not be prescribed to patients who test positive for the allele due to the increased risk of SCAR.(1) In addition, guidelines developed by the 2012 American College of Rheumatology for Management of Gout recommend that HLA-B*58:01 testing should be considered in select patient subpopulations at an elevated risk for allopurinol-induced SCAR. Those of Korean descent, especially those with stage 3 or higher chronic kidney disease, or of Han Chinese or Thai descent, irrespective of renal function, should be tested.(2)

**Useful For:** Identifying individuals with an increased risk of severe cutaneous adverse reactions to allopurinol based on the presence of the human leukocyte antigen HLA-B*58:01 allele

**Interpretation:** Positivity for HLA-B*58:01 confers increased risk for hypersensitivity to allopurinol. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenetic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HLA-B*5801 Genotype, Allopurinol Hypersensitivity, Saliva**

**Clinical Information:** The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*58:01 allele. Frequency of the HLA-B*58:01 allele varies with ethnicity, with a frequency of 6% to 7% in Asian populations, and 1% in Caucasian populations. Allopurinol is a drug widely used for hyperuricemia-related diseases such as gout, Lesch-Nyhan syndrome, and recurrent urate kidney stones. However, this drug is one of the most common causes of severe cutaneous adverse reactions (SCAR), an umbrella term encompassing drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These reactions have a reported mortality rate of 20% to 25%. For individuals taking allopurinol, the presence of the HLA-B*58:01 allele has been strongly associated with allopurinol-induced SCAR. Guidelines from the Clinical Pharmacogenomics Implementation Consortium (CPIC) recommend HLA-B*5801 genotyping be performed when considering prescribing allopurinol, and that allopurinol should not be prescribed to patients who test positive for the allele, due to the increased risk of SCAR.(1) In addition, guidelines developed by the 2012 American College of Rheumatology for Management of Gout recommend that HLA-B*5801 testing should be considered in select patient subpopulations at an elevated risk for allopurinol-induced SCAR. Those of Korean descent, especially those with stage 3 or higher chronic kidney disease, or of Han Chinese or Thai descent, irrespective of renal function, should be tested.(2)

**Useful For:** Identifying individuals with an increased risk of severe cutaneous adverse reactions to allopurinol based on the presence of the human leukocyte antigen HLA-B*58:01 allele Genotyping
patients who prefer not to have venipuncture done

**Interpretation:** Positivity for HLA-B*5801 confers increased risk for hypersensitivity to allopurinol. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HLA-B27, Blood**

**Clinical Information:** This major histocompatibility coded class I antigen is associated with ankylosing spondylitis, juvenile rheumatoid arthritis, and Reiter syndrome. The mechanism of the association is not understood but probably is that of linkage disequilibrium. There is an increased prevalence of HLA-B27 in certain rheumatic diseases, particularly ankylosing spondylitis. Studies have demonstrated that the B*27:06 allele, which is present in a small percentage of individuals of Asian ethnicity, may not be associated with ankylosing spondylitis.

**Useful For:** Assisting in the diagnostic process of ankylosing spondylitis, juvenile rheumatoid arthritis, and Reiter syndrome

**Interpretation:** Approximately 8% of the normal population carries the HLA-B27 antigen. HLA-B27 is present in approximately 89% of patients with ankylosing spondylitis, 79% of patients with Reiter syndrome, and 42% of patients with juvenile rheumatoid arthritis. However, lacking other data, it is not diagnostic for these disorders.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HMBSZ, HMBS Gene, Full Gene Analysis**

**Clinical Information:** Hydroxymethylbilane synthase (HMBS) deficiency is an autosomal dominant disorder with incomplete penetrance that can present as acute intermittent porphyria (AIP). The most common clinical presentation of AIP is abdominal pain. Acute attacks can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HMBS deficiency can also be without clinical or biochemical manifestations. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco and cannabis. The measurement of porphobilinogen deaminase (PBG-D) enzyme activity in erythrocytes facilitates detection of AIP during latent periods, and also confirms a biochemical diagnosis during acute episodes. However, a normal result does not completely exclude a diagnosis of HMBS deficiency/AIP. The preferred diagnostic test is molecular genetic testing of the HMBS gene.
**Useful For:** Confirming a diagnosis of hydroxymethylbilane synthase deficiency/acute intermittent porphyria

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Homocysteine (Total), Methylmalonic Acid, and Methylcitric Acid, Blood Spots**

**Clinical Information:** Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 350,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, mental retardation, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine (free and total) along with decreased concentrations of cystine. Methylmalonic acidemia (MMA) and propionic acidemia (PA) are defects of propionate metabolism caused by deficiencies in methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMA includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal methylmalonic acid concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Newborn screening for inborn errors of methionine and propionic acid metabolism relies on elevations of methionine and propionyl carnitine. These analytes are not specific for these conditions and are prone to false-positive results, leading to increased cost, stress, and anxiety for families who are subjected to follow-up testing. Homocysteine, methylmalonic acid, and methylcitric acid are more specific markers for inborn errors of methionine and propionic acid metabolism. Molecular genetic testing can be used to confirm a biochemical diagnosis for homocystinuria, methylmalonic acidemia, and propionic acidemia.

**Useful For:** Second-tier assay of newborn screening specimens when abnormal propionyl carnitine or methionine concentrations are identified in a primary newborn screen

**Interpretation:** Elevated homocysteine, methylcitric acid, or methylmalonic acid concentrations are indicative of an underlying metabolic disorder. In a Mayo study that analyzed 200 unaffected neonates, clear clinical discrimination was observed when compared to patients with defects of propionate or methionine metabolism. The 99.5 percentile, determined from the analysis of 200 dried blood spots of unaffected controls, for methylmalonic acid (MMA), methylcitric acid (MCA), and homocysteine (HCY), are 1.58 nmol/mL, 0.62 nmol/mL, and 9.9 nmol/mL, respectively, providing clear clinical discrimination from patients with defects of propionate or methionine metabolism (eg, methylmalonic acidemia: MMA=31.9 nmol/mL; propionic acidemia: MCA=12.8 nmol/mL; homocystinuria: HCY=189 nmol/mL).

**Reference Values:**
Homocysteine: <15.0 nmol/mL
Methylmalonic acid: <5.0 nmol/mL
Methylcitric acid: <1.0 nmol/mL
An interpretive report will also be provided.


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**Homocysteine, Total, Plasma**

**Clinical Information:** Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Genetic defects in vitamin cofactors (vitamin B6, B12, and folate) and nutritional deficiency of B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency, and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine was also thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following FDA-mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

**Useful For:** An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants: Methionine synthase deficiency -Cobalamin (Cbl) metabolism: Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency: Adenosylhomocysteinate (AHCY) deficiency -Glycine N-methyltransferase (GNMT) deficiency -Methionine adenosyltransferase (MAT) I/III deficiency

**Interpretation:** Homocysteine concentrations >13 mcmol/L are considered abnormal in patients evaluated for suspected nutritional deficiencies (B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between B12 (cobalamin) and folate deficiencies, as MMA is only elevated in B12 deficiency. Response to dietary treatment can be evaluated by monitoring plasma homocysteine concentrations over time. Homocysteine concentrations < or =10 mcmol/L are desirable when utilized for cardiovascular risk.

**Reference Values:**
Adults: < or =13 mcmol/L

Reference values apply to fasting specimens only.

**Homocysteine, Total, Serum**

**Clinical Information**: Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocysteinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine re-methylation. Genetic defects in vitamin cofactors (vitamin B6, B12, and folate) and nutritional deficiency of B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency, and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine also was thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following FDA-mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

**Useful For**: An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants -Methionine synthase deficiency -Cobalamin (Cbl) metabolism: -Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency -Adenosylhomocysteinase (AHCY) deficiency -Glycine N-methyltransferase (GNMT) deficiency -Methionine adenosyltransferase (MAT) I/III deficiency

**Interpretation**: Homocysteine concentrations >13 mcg/mL are considered abnormal in patients evaluated for suspected nutritional deficiencies (B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between B12 (cobalamin) and folate deficiencies, as MMA is only elevated in B12 deficiency. Response to dietary treatment can be evaluated by monitoring serum homocysteine concentrations over time. Homocysteine concentrations < or =10 mcg/mL are desirable when utilized for cardiovascular risk.

**Reference Values**: 
Adults: < or =13 mcg/mL

Reference values apply to fasting specimens only.


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**Homocysteine, Total, Urine**

**Clinical Information**: To be used in conjunction with plasma amino acids and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism. Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia/uria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine re-methylation. Homocysteine also was thought to be an independent predictor of cardiovascular disease.
(atherosclerosis, heart disease, thromboembolism), as early observational studies prior to 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following FDA-mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet.

**Useful For:** As an aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (Homocystinuria) -Methenyltetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants: - Methionine synthase deficiency -Cobalamin (Cbl) Metabolism: - Combined Methyl-Cbl and Adenosyl-Cbl deficiencies: Cbl C2, Cbl D2 and Cbl F3 deficiencies - Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E and Cbl G deficiencies -Transcobalamin II deficiency: - Adenosylhomocysteinase: AHcy deficiency - Glycine N-methyltransferase: GNMT deficiency - Methionine Adenosytransferease I/III Deficiency: MAT I/III deficiency As a (weak) indicator of cardiovascular risk

**Interpretation:** Hyperhomocysteinuria could be caused by either genetic or nutritional factors. While the highest levels are characteristic of classic homocystinuria, there are no reliable cut-offs to differentiate between genetic or dietary causes of elevated homocysteine (Hcy) levels. In our experience, very high Hcy levels have been seen in some patients with cystathione beta-synthase deficiency. Hcy levels >9 mcMol/g creatinine are considered abnormal in patients under evaluation for cardiovascular or neurovascular disease.

**Reference Values:**
Adults: 0-9 mcMol/g creatinine


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**HVA**

**Homovanillic Acid (HVA), 24 Hour, Urine**

**Clinical Information:** Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid [VMA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** Screening children for catecholamine-secreting tumors with a 24-hour urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

**Interpretation:** Vanillylmandelic acid (VMA) and/or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monamine oxidase-A deficiency.

**Reference Values:**
<1 year: <35.0 mg/g creatinine

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Homovanillic Acid (HVA), Random, Urine

**Clinical Information:** Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid [VMA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** Screening children for catecholamine-secreting tumors with a random urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

**Interpretation:** Vanillylmandelic acid and/or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monamine oxidase-A deficiency.

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<table>
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<tr>
<th>Age</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>&lt;35.0 mg/g creatinine</td>
</tr>
<tr>
<td>1 year</td>
<td>&lt;30.0 mg/g creatinine</td>
</tr>
<tr>
<td>2-4 years</td>
<td>&lt;25.0 mg/g creatinine</td>
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<tr>
<td>5-9 years</td>
<td>&lt;15.0 mg/g creatinine</td>
</tr>
<tr>
<td>10-14 years</td>
<td>&lt;9.0 mg/g creatinine</td>
</tr>
<tr>
<td>&gt; or =15 years (adults)</td>
<td>&lt;8.0 mg/g creatinine</td>
</tr>
</tbody>
</table>

Honey, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>IgE kU/L</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
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<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages.


Honeybee Venom, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Hop Fruit, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**HBEA 82484**

**Hornbeam, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**HORS 82874**

**Horse Dander, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**HORM 82375**

**Horse Meat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**HSPR 82134**

**Horse Serum Proteins, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
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**Horsefly/Stablefly, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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FHORS
Horseradish (Armoracia rusticana/A.lapathifolia) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€” 0.69 Low Positive 2 0.70 â€” 3.49 Moderate Positive 3 3.50 â€” 17.49 Positive 4 17.50 â€” 49.99 Strong Positive 5 50.00 â€” 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

DF
House Dust Mites/Dermatophagoides farinae, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
House Dust Mites/Dermatophagoides pteronyssinus, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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House Dust/Greer Lab, IgE

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**House Dust/H-S Lab, IgE**

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HOXB13 Mutation Analysis (G84E)

Clinical Information: The HOXB13 gene is a homeobox transcription factor involved in normal prostate development and is a key determinant in response to androgens. Recently, a novel germline mutation in the HOXB13 gene, G84E, has been found to be associated with an up to 3- to 5-fold increased risk of prostate cancer. The G84E mutation has been shown to be overrepresented in the disease population, and carriers of the G84E mutation may develop prostate cancer at an earlier age than noncarriers. However, the G84E mutation has been seen in both family members with prostate cancer and in healthy relatives, indicating reduced penetrance. Also, in families carrying the G84E mutation, prostate cancer has been reported in nonmutation carriers.

Useful For: Determining whether the clinical phenotype of prostate cancer is due to the G84E mutation in the HOXB13 gene in the affected individual Predictive testing and familial risk assessment when the G84E mutation in the HOXB13 gene has been identified in an affected family member

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


HPV Reflex ThinPrep Pap Test

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, non-enveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once
the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and/or biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women that are positive for HR-HPV but negative by routine cytology. Women that are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women that are negative for genotypes 16 and/or 18 may have repeat cytology and HR HPV testing in 12 months.(1) Recently, the Food and Drug Administration (FDA) approved the use of the Roche Cobas HPV test for primary screening of cervical/endocervical samples collected in ThinPrep/PreservCyt media. In addition, the age at which patients may be screened by the HPV test dropped from 30 years to 25 years old.

**Useful For:** Screening for infection with high-risk (HR) human papillomavirus associated with the development of cervical cancer Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present

**Interpretation:** Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Clinical References:**

**HTLV I/II DNA, Qualitative Real-Time PCR**

**Reference Values:**
Reference Range: Not Detected
**Human Anti-mouse Antibody (HAMA)**

**Reference Values:**

< or = 74 ng/mL

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**Human Chorionic Gonadotropin (hCG), Quantitative, Pregnancy, Serum**

**Clinical Information:** Human chorionic gonadotropin (hCG) is a glycoprotein hormone that consists of 2 subunits (alpha and beta chains), which are associated to comprise the intact hormone. The alpha subunit is similar to those of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. The beta subunit of hCG differs from other pituitary glycoprotein hormones, which results in its unique biochemical and immunological properties. This method quantitates the sum of intact hCG plus the beta subunit. hCG is produced in the placenta during pregnancy. In nonpregnant women, it can also be produced by tumors of the trophoblast, germ cell tumors with trophoblastic components, and some nontrophoblastic tumors. The biological action of hCG serves to maintain the corpus luteum during pregnancy. It also influences steroid production. The serum in pregnant women contains mainly intact hCG. Measurement of the hCG concentration permits the diagnosis of pregnancy as early as 1 week after conception.

**Useful For:** Early detection of pregnancy Investigation of suspected ectopic pregnancy or other pregnancy-related complications Monitoring in vitro fertilization patients

**Interpretation:** Values between 5 and 25 IU/L are indeterminate for pregnancy. Consider confirming with repeat test in 72 hours. Values in pregnancy should double every 3 days for the first 6 weeks. Elevated concentrations of human chorionic gonadotropin (hCG) measured in the first trimester of pregnancy are observed in normal pregnancy, but may serve as an indication of choriocarcinoma, hydatiform mole, or multiple pregnancy. Decreasing hCG concentrations indicate threatened or missed abortion, recent termination of pregnancy, ectopic pregnancy, gestosis or intrauterine death. Both normal and ectopic pregnancies generally yield positive results of pregnancy tests. The comparison of quantitative hCG measurements with the results of transvaginal ultrasonography (TVUS) may aid in the diagnosis of ectopic pregnancy. When an embryo is first large enough for the gestation sac to be visible on TVUS, the patient generally will have hCG concentrations between 1,000 and 2,000 IU/L. (These are literature values. Definitive values for this method have not been established at this time.) If the hCG value is this high and no sac is visible in the uterus, ectopic pregnancy is suggested. Elevated values will also be seen with choriocarcinoma and hydatiform mole. Peri- and postmenopausal females may have detectable hCG concentrations (<14 IU/L) due to pituitary production of hCG. Serum follicle stimulating hormone measurement may aid in ruling out pregnancy in this population. Cutoffs of >20 to 45 IU/L have been suggested and are method dependent.

**Reference Values:**

Negative: <5 IU/L

Indeterminate: 5-25 IU/L

Positive: >25 IU/L

Suggest repeat testing of indeterminate results in 72 hours.


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**Human Epididymis Protein 4, Serum**

**Clinical Information:** Human epididymis protein 4 (HE4) belongs to the family of whey acidic four-disulfide core proteins. Currently, the biologic function of HE4 is unknown. HE4 has been shown to be overexpressed in 93% of serous, 100% of endometrioid, and 50% of clear cell ovarian carcinomas. In a study of 233 patients with a pelvic mass, including 67 with epithelial ovarian cancer, HE4 had a higher sensitivity for ovarian cancer detection than cancer antigen 125 (CA 125), 72.9% versus 43.3%.
respectively, at a specificity of 95%. Researchers also found HE4 to be elevated in more than half of the ovarian cancer patients who did not have elevated CA 125 levels; therefore, the combination of markers provided slightly improved cancer diagnostic sensitivity for the detection of ovarian cancer. The main established application of HE4 is in post-therapy monitoring of ovarian cancer patients, who had elevated pretreatment levels. In this setting, it complements CA 125 measurement and facilitates follow-up of patients with little or no CA 125 pretreatment elevations. Certain histological types of ovarian cancer (mucinous or germ cell tumors) rarely express HE4, therefore the use of HE4 is not recommended for monitoring of patients with these types of ovarian cancer.

**Useful For:** An aid in monitoring patients with treated epithelial ovarian cancer for recurrence or progression

**Interpretation:** Increase in human epididymis protein 4 (HE4) suggests recurrence or disease progression, while a decrease suggests therapeutic response. A change in serum HE4 concentration of > or =20% is considered significant.

**Reference Values:**
- Females: < or =140 pmol/L
- Males: Not applicable

**Clinical References:**

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**Human Herpesvirus 6 (HHV-6A and HHV-6B) by Quantitative PCR**

**Reference Values:**
Not detected

The quantitative range of this assay is 3.0–6.0 log copies/mL (1,000 - 999,000 copies/mL).

A negative result (less than 3.0 log copies/mL or less than 1,000 copies/mL) does not rule out the presence of PCR inhibitors in the patient specimen or HHV6 DNA in concentrations below the level of detection of the test. Inhibition may also lead to underestimation of viral quantitation.

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**Human Herpesvirus-6, Molecular Detection, PCR, Plasma**

**Clinical Information:** Herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These viruses contain DNA surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV] 1, HSV 2, varicella zoster virus [VZV], CMV, Epstein-Barr virus [EBV], HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections subsequent to latent association with cells. Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. HHV-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the virus has been associated with central nervous system disease almost exclusively in immunocompromised patients. HHV-6 is commonly detected in patients posttransplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, encephalitis, and bone marrow suppression. However, the majority of HHV-6 infections are asymptomatic. The incidence of HHV-7 infection and its clinical manifestations posttransplantation are less well characterized. HHV-6 is designated as variant A (HHV-6A) or variant B (HHV-6B) depending on restriction enzyme digestion patterns and on its reaction with monoclonal antibodies. Generally, variant B has been associated with exanthem subitum, whereas variant A has been found in many immunosuppressed patients.
**Useful For:** As an adjunct in the rapid diagnosis of human herpesvirus-6 infection

**Interpretation:** A positive result indicates the presence of specific DNA from human herpesvirus-6 (HHV-6) and supports the diagnosis of infection with this virus. A negative result indicates the absence of detectable DNA from HHV-6 in the specimen, but it does not negate the presence of the virus or active or recent disease.

**Reference Values:**
Negative

**Clinical References:**

**HHV6V**

**Human Herpesvirus-6, Molecular Detection, PCR, Varies**

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**Useful For:** As an adjunct in the rapid diagnosis of human herpesvirus-6 infection

**Reference Values:**
Negative

**Clinical References:**

**FHMPV**

**Human Metapneumovirus (hMPV) RNA**

**Reference Values:**
Reference Range: Not Detected

**HPVP**

**Human Papillomavirus (HPV) DNA Detection with Genotyping, High Risk Types by PCR with Papanicolaou Smear Reflex, ThinPrep**
Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for "other" HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV, but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and/or 18 may have repeat cytology and HR-HPV testing in 12 months. Recently, the Food and Drug Administration (FDA) approved the use of the Roche Cobas HPV test for primary screening of cervical and endocervical samples collected in ThinPrep/PreservCyt media. In addition, the age at which patients may be screened by the HPV test dropped from 30 to 25 years old.

**Useful For:** Screening for infection with high-risk (HR) human papillomavirus associated with the development of cervical cancer

**Interpretation:** HPV with Genotyping PCR: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR)-HPV, consider referral for colposcopy, if clinically indicated. For women aged 25 years and older who are positive for HPV-16 and/or HPV-18, but negative by Pap smear, consider referral for colposcopy, if clinically indicated. Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Reference Values:**

HPV with Genotyping PCR: Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
ThinPrep Pap Test: Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.


**SHPV**

**Human Papillomavirus (HPV) DNA Detection with Genotyping, High-Risk Types by PCR, SurePath**

**Clinical Information:** Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, non-enveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(1-3) Although persistent infection with HR HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and/or biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate
follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that
the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence
interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for ‘other’
HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(4) Based in part on
these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that
HPV 16/18 genotyping be performed on women that are positive for HR-HPV but negative by routine
cytology. Women that are found to be positive for HPV-16 and/or -18 may be referred to colposcopy,
while women that are negative for genotypes 16 and/or 18 may have repeat cytology and HR HPV testing
in 12 months.(1)

Useful For: Detection of high-risk (HR) genotypes associated with the development of cervical cancer
An aid in triaging women with abnormal Pap smear results Individual genotyping of human
papillomavirus (HPV)-16 and/or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can be
used as an aid in triaging women with positive HR-HPV but negative Pap smear results.

Interpretation: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1
or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative
result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous
cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR)
HPV, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a
negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for
colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear,
positive HR HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by
both cytology and a HR HPV test in 12 months.

Reference Values:
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology
Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. J Low Genit Tract Dis
Procedure manual and package insert: cobas HPV test. Roche Diagnostics. Indianapolis, IN, version
05641268001-01EN 6. Gilbert L, Oates E, Ratnam S. Stability of cervical specimens in SurePath medium
for HPV testing with the Roche cobas 4800. J Clin Microbiol 2013 Oct;51(10):3412-3414

Human Papillomavirus (HPV) DNA Detection with Genotyping,
High-Risk Types by PCR, ThinPrep

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of
cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has
been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded
DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types
of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However,
data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68)
are considered high risk (HR) for the development of cervical cancer and its precursor lesions.
Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with
progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately
60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical
cancers.(1-3) Although persistent infection with HR HPV is necessary for the development of cervical
cancer and its precursor lesions, only a very small percentage of infections progress to these disease
states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all
women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN, although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes, and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV-negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(1)

**Useful For:** Detection of high-risk (HR) genotypes associated with the development of cervical cancer

Aids in triaging women with abnormal Pap smear results

Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can aid in triaging women with positive HR-HPV but negative Pap smear results

**Interpretation:** A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive-HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

**Reference Values:**

Negative for human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

**Clinical References:**

Human Papillomavirus (HPV) High Risk E6/E7, RNA In Situ Hybridization

Clinical Information: This assay is intended to identify the presence of human papillomavirus (HPV) E6/E7 transcripts from high-risk genotypes. This test has been shown to be more sensitive than HPV DNA in situ hybridization (ISH). Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC. An indication for this test is p16 expression by immunohistochemistry and negative HPV DNA ISH. In this instance, consideration should be given to the possibility of a false-negative HPV DNA ISH result.

Useful For: Stratification of oropharyngeal squamous cell carcinoma

Interpretation: This test will be processed as a special procedure in combination with 80172 / Human Papillomavirus (HPV) Typing, DNA In Situ Hybridization or 60483 / Human Papillomavirus (HPV), High-Risk, DNA In Situ Hybridization. If additional interpretation/analysis is needed, order 70012 / Pathology Consultation along with this test.

Reference Values:
Results are reported as positive or negative for types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82.

Clinical References:

Human Papillomavirus (HPV) Typing, DNA In Situ Hybridization

Clinical Information: Human papillomavirus (HPV) infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas. Persistent infections with high-risk genotypes (16, 18, 31, 33, and 51) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

Useful For: Detection of both low-risk (6, 11) and high-risk genotypes (16, 18, 31, 33, and 51) of human papillomavirus DNA in paraffin-embedded human tissue

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation/analysis is needed, please request test 70012 / Pathology Consultation along with this test.

Reference Values:
Results are reported as positive or negative for low-risk genotypes 6, 11, and/or high-risk genotypes 16, 18, 31, 33, and 51.

If additional interpretation/analysis is needed, request 70012 / Pathology Consultation along with this test.

Clinical References:
Human Papillomavirus (HPV), High-Risk, DNA In Situ Hybridization

**Clinical Information:** Persistent infections with high risk human papillomavirus (HPV) genotypes (16, 18, 31, 33 and 51) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

**Useful For:** Detection of human papillomavirus DNA from high-risk genotypes (16, 18, 31, 33 and 51)

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation/analysis is needed, please request test 70012 / Pathology Consultation along with this test.

**Clinical References:**

Human Papillomavirus (HPV), Low-Risk, DNA In Situ Hybridization

**Clinical Information:** Human papillomavirus infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas.

**Useful For:** Detection of human papillomavirus (HPV) DNA from low-risk genotypes (6, 11)

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation/analysis is needed, please request test 70012 / Pathology Consultation along with this test.

**Clinical References:**

Human Placental Lactogen (HPL)

**Reference Values:**
- Males and nonpregnant Woman: 0.00 - 0.10 mcg/mL
  - 1st Trimester of Pregnancy: 0.20 - 2.10 mcg/mL
  - 2nd Trimester of Pregnancy: 0.50 - 6.70 mcg/mL
  - 3rd Trimester of Pregnancy: 4.50 - 12.80 mcg/mL

Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/-II) Antibody Confirmation, Serum
Clinical Information: Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. HTLV-I infection is endemic in southwestern Japan, Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I infection: adult T-cell leukemia or lymphoma (ATL), and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis also have been reported in HTLV-I-infected patients. HTLV-II is prevalent among injection drug users in the United States and in Europe, and >80% of HTLV infections in drug users in the United States are due to HTLV-II. HTLV-II also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as EIA. For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Confirmatory detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in human serum specimens that are consistently reactive by initial screening tests Differentiating between HTLV-I- and HTLV-II-specific IgG antibodies This confirmatory assay should be ordered only on specimens that are consistently reactive by anti-HTLV-I/-II screening assays (see HTLV/I / Human T-Cell Lymphotropic Virus Types I and II [HTLV-I/-II] Antibody Screen with Confirmation, Serum).

Interpretation: Negative confirmatory test results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in serum. A reactive screening (EIA) result with a negative or indeterminate confirmatory (line immunoassay) test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection. Positive results for HTLV-I antibodies indicate the confirmed presence of HTLV-I IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-I and p19-I band intensity is greater than the gp46-II band intensity. Positive results for HTLV-II antibodies indicate the confirmed presence of HTLV-II IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the gp46-II band intensity is a) greater than the gp46-I band intensity and b) > or =the sum of the gp46-I and p19-I band intensity. Indeterminate results indicate the presence of gp21-I/-II band only or combination of any 2 bands without a detectable gp21-I/-II band. Patients with indeterminate test results with known risk factors for HTLV-I or HTLV-II infection should undergo repeat confirmatory antibody testing in 1 to 2 months to determine final infection status. Differentiation of HTLV-I and HTLV-II infection is not possible (ie, nontypeable HTLV antibodies) when the band intensity pattern does not meet the criteria of positive HTLV-I or HTLV-II antibody band intensity pattern.

Reference Values:
Negative
This confirmatory assay should be ordered only on specimens that are reactive by an anti-HTLV-I/-II screening immunoassay.
Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/-II) Antibody Screen with Confirmation, Serum

Clinical Information: Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. HTLV-I infection is endemic in southwestern Japan, Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I infection: adult T-cell leukemia or lymphoma, and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy or tropical spastic paraparesis. Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis also have been reported in HTLV-I-infected patients. HTLV-II is prevalent among injection drug users in the United States and in Europe, and >80% of HTLV infections in drug users in the United States are due to HTLV-II. HTLV-II also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as EIA. For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Qualitative detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific antibodies with confirmation and differentiation between HTLV-I and HTLV-II infection

Interpretation: Negative screening results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I- and HTLV-II)-specific IgG antibodies in serum. A reactive screening test result is suggestive of infection with either HTLV-I or HTLV-II. However, this result does not confirm infection (eg, low specificity), and it cannot differentiate between HTLV-I and HTLV-II infection. Specimens with reactive screening test results will be tested automatically by the line immunoassay (LIA) confirmatory test. Positive LIA results provide confirmatory evidence of infection with HTLV-I or HTLV-II. A reactive screening result with a negative or indeterminate confirmatory test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection.

Reference Values:

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**Humoral Immunity Evaluation Panel**

**Reference Values:**

**Humoral Immunity Evaluation**

**Diphtheria Antitoxoid**

Reference Range: > or =0.01 IU/mL (Post-Vaccination)

Interpretive Criteria:
- <0.01 IU/mL Nonprotective Antibody Level
- > or =0.01 IU/mL Protective Antibody Level

This test was developed and its performance characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.

**Haemophilus influenzae Type B Antibody (IgG)**

Reference Range: > or =1.00 mcg/mL post-vaccination (protective level)

Interpretive Criteria:
- <0.15 mcg/mL Nonprotective Antibody Level
- 0.15 - 0.99 mcg/mL Indeterminate for protective antibody
- > or =1.0 mcg/mL Protective Antibody Level

IgG antibody to polyribosylribitol phosphate (PRP), the capsular polysaccharide of Haemophilus influenzae type b, is measured in micrograms/mL (mcg/mL), based on correlations with a reference Farr radioimmunoprecipitation assay (RIA). The exact level of antibody needed for protection from infection has not been clarified; values ranging from 0.15 mcg/mL to 1.0 mcg/mL have been reported. A four-fold increase in the PRP IgG antibody level between pre-vaccination and post-vaccination sera is considered evidence of effective immunization.

**Tetanus Antitoxoid**

Reference Range: > or =0.50 IU/mL (Post-Vaccination)

Interpretive Criteria:
- <0.05 IU/mL Nonprotective Antibody Level
- 0.05 - 0.49 IU/mL Indeterminate for Protective Antibody
- > or =0.50 IU/mL Protective Antibody Level

Levels greater than or equal to 0.50 IU/mL are generally considered protective, whereas levels less than 0.05 IU/mL indicate a lack of protective antibody. Levels between 0.05 and 0.49 IU/mL are indeterminate for the presence of protective antibody and may indicate a need for further immunization to tetanus toxoid.

This test was developed and its performance characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.
### Hunter Syndrome, Full Gene Analysis

**Clinical Information:** Mucopolysaccharidosis type II (MPS-II), also known as Hunter syndrome, is a rare X-linked condition caused by mutations in the IDS gene. MPS-II is characterized by reduced or absent activity of the iduronate 2-sulfatase enzyme. The clinical features and severity of symptoms of MPS-II are widely variable, ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, joint contractures, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. Female carriers are usually asymptomatic. The IDS gene is located on the X chromosome and has 9 exons. IDS is the only known gene to be associated with MPS-II. The recommended first-tier test for MPS-II is biochemical testing that measures iduronate 2-sulfatase enzyme activity in fibroblasts: IDNS / Iduronate Sulfatase, Fibroblasts. Individuals with decreased or absent enzyme activity are more likely to have a mutation in the IDS gene identifiable by molecular gene testing. However, enzymatic testing is not reliable to detect carriers. This test screens for mutations in all 9 exons of the IDS gene.

**Useful For:** Confirmation of a diagnosis of mucopolysaccharidosis type II (Hunter syndrome) Carrier testing when there is a family history of mucopolysaccharidosis type II (Hunter syndrome), but disease-causing mutations have not been previously identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.

**Reference Values:** An interpretive report will be provided.

HAD 35452

Huntington Disease, Molecular Analysis

Clinical Information: Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder caused by a CAG repeat expansion in the HTT gene. HD is associated with cognitive impairment leading to dementia and a wide range of neuropsychiatric problems including apathy, depression, anxiety, and other behavioral disturbances. Additionally, affected individuals typically develop extrapyramidal symptoms (eg, dystonia, dysarthria, chorea, gait disturbance, postural instability, oculomotor dysfunction).

Useful For: Molecular confirmation of clinically suspected cases of Huntington disease (HD) Presymptomatic testing for individuals with a family history of HD and a documented expansion in the HTT gene

Interpretation: An interpretive report will be provided.

Reference Values:
Normal alleles: <27 CAG repeats
Intermediate alleles: 27-35 CAG repeats
Reduced penetrance: 36-39 CAG repeats
Full penetrance: >39 CAG repeats
An interpretive report will be provided.


MPS1Z 35465

Hurler Syndrome, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type I (MPS-I) can be categorized into 3 syndromes, Hurler syndrome, Scheie syndrome, and Hurler-Scheie syndrome. MPS-I, inherited in an autosomal recessive manner, is caused by mutations in the IDUA gene. Furthermore, MPS-I is characterized by reduced or absent activity of the alpha-L-iduronidase enzyme. Hurler syndrome (severe MPS-I) has early onset and consists of skeletal deformities, coarse facial features, corneal clouding, hepatosplenomegaly, cardiac involvement, hearing loss, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. Hurler-Scheie syndrome and Scheie syndrome (attenuated MPS-I) have onset between 3 to 10 years of age and consist of corneal clouding, cardiac involvement, moderate-to-severe hearing loss, and progressive pulmonary disease. Typically skeletal and joint involvement is the most significant source of discomfort for attenuated MPS-I. Intellect with attenuated MPS-I is typically normal or nearly normal. The IDUA gene is located on chromosome 4 and has 14 exons. IDUA is the only known gene to be associated with MPS-I, and the 3 syndromes appear to be caused by different combinations of mutations. The recommended first-tier test for MPS-I is biochemical testing that measures alpha-L-iduronidase enzyme activity in blood or fibroblasts: IDSWB / Alpha-L-Iduronidase, Blood or IDST / Alpha-L-Iduronidase, Fibroblasts. Individuals with decreased or absent enzyme activity are more likely to have 2 identifiable mutations in the IDUA gene by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers.

Useful For: Identifying mutations within the IDUA gene Confirmation of a diagnosis of...
mucopolysaccharidosis type I (MPS-I) Carrier testing when there is a family history of MPS-I, but disease-causing mutations have not been previously identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
5. Vijay S, Wraith JE: Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. Acta Paediatr 2005;94(7):872-877

**Hydrocodone and metabolites**

**Reference Values:**
Reference Range:
- Hydrocodone, unconjugated: 10–100 ng/mL
- Hydromorphone, unconjugated: 1–30 ng/mL
- Dihydrocodeine, unconjugated: Not established ng/mL

**Hydrocodone with Metabolite Confirmation, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone).
Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the 6 beta hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6 hydroxy reduction metabolites. The presence of hydromorphone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone, therefore the presence of hydromorphone could also indicate exposure to hydrocodone.

**Useful For:** Detection and quantification of hydrocodone and hydromorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**
Negative
Cutoff concentrations:
- Hydrocodone: 100 ng/mL
- Hydromorphone: 100 ng/mL

**Clinical References:**
1. Gutstein HB, Akil H: Opioid Analgesics. In The Pharmacological Basis of
Hydromorphone Confirmation, Urine

Clinical Information: Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone). Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the 6 beta hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6 hydroxy reduction metabolites. The presence of hydromorphone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone, therefore the presence of hydromorphone could also indicate exposure to hydrocodone.

Useful For: Detection and quantification of hydromorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative
Cutoff concentrations:
Hydromorphone: 100 ng/mL


Hydroxychloroquine, Serum/Plasma

Reference Values:
Reporting limit determined each analysis.

Synonym(s): Plaquenil; Oxychloroquine

Peak plasma concentrations of 410 +/- 130 ng/mL were achieved 2.4 hours after single oral dose of 400 mg hydroxychloroquine (n = 6). Two cases of hydroxychloroquine overdose (20 g each) were successfully treated throughout cardiovascular collapse and had serum concentrations of 14000 and 26000 ng/mL.

Hydroxycorticosterone, 18

Reference Values:
If no age provided:

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28 Weeks)</td>
<td>10-670</td>
</tr>
<tr>
<td>Premature (31-35 Weeks)</td>
<td>57-410</td>
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</table>
Clinical Information: Acylcarnitine analysis is included in newborn screening blood testing and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxy glutaric acid (2OH-GA), 3-hydroxy glutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by LC-MS/MS allows better differentiation among C4-acylcarnitine and glutarylcarnitine/C10-OH isomers. C4-acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short-chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive; there is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1, also known as glutaric aciduria type 1, is caused by a deficiency of glutaryl-CoA dehydrogenase. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often as a result of acute neurologic crises triggered by illness. Individuals with GA-1 typically show elevations of glutaric acid and 3OH-GA, even in those considered to be “low excretors.” Glutaric acidemia (GA-2), also known as multiple acyl-CoA
dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA-2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in glutaric acid, individuals with GA-2 can also show increased EMA, MSA, 2OH-GA, and 3OH-GA. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see http://www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) Evaluation of patients with abnormal newborn screens showing elevations of C4-acylcarnitine to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aids in diagnosis of glutaric acidemia type 2

**Interpretation:** Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short-chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxy glutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type 1 (GA-1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type 2.

**Reference Values:**
- 2-OH Glutaric acid < or =25 nmol/mL
- 3-OH Glutaric acid < or =1.5 nmol/mL
- Glutaric acid < or =1.5 nmol/mL
- Methylsuccinic acid < or =0.45 nmol/mL
- Ethylmalonic acid < or =3.5 nmol/mL


**HGEMP 62300 Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid, and Methylsuccinic Acid, Plasma**

**Clinical Information:** Acylcarnitine analysis is included in newborn screening blood testing and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxy glutaric acid (2OH-GA), 3-hydroxy glutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by LC-MS/MS allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers. C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive; there is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals...
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Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) Evaluation of patients with abnormal newborn screens showing elevations of C4- acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aids in diagnosis of glutaric acidemia type 2

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Reference Values:
2-OH Glutaric acid < or =4.5 nmol/mL
3-OH Glutaric acid < or =0.7 nmol/mL
Glutaric acid < or =0.8 nmol/mL
Methylsuccinic acid < or =0.3 nmol/mL
Ethylmalonic acid < or =1.5 nmol/mL

ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive; there is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutaryl carnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1, also known as glutaric aciduria type 1, is caused by a deficiency of glutaryl-CoA dehydrogenase. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often as a result of acute neurologic crises triggered by illness. Individuals with GA-1 typically show elevations of glutaric acid and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia (GA-2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA-2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood, and muscle weakness in childhood and adulthood. In addition to elevations in glutaric acid, individuals with GA-2 can also show increased EMA, MSA, 2OH-GA, and 3OH-GA. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see http://www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutaryl carnitine (C5-DC) Evaluation of patients with abnormal newborn screens showing elevations of C4 acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aids in diagnosis of glutaric acidemia type 2

Interpretation: Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl-CoA dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxy glutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type 1 (GA-1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia (GA-2).

Reference Values:
2-OH Glutaric acid < or =4.5 nmol/mL
3-OH Glutaric acid < or =0.7 nmol/mL
Glutaric acid < or =1.5 nmol/mL
Methylsuccinic acid < or =0.3 nmol/mL
Ethylmalonic acid < or =1.5 nmol/mL


Hydroxyzine (Vistaril, Atarax), Serum

Reference Values:
Reference Range: 10 - 100 ng/mL

FVIST 90121

Hydroxyzine (Vistaril, Atarax), Serum

Reference Values:
Reference Range: 10 - 100 ng/mL
Hyperimmunoglobulin M (Hyper-IgM) Defects Panel

Clinical Information: Hyperimmunoglobulin M (hyper-IgM) syndromes are a collection of primary humoral immunodeficiencies characterized by recurrent infections along with low serum IgG and IgA, and normal or elevated IgM. Over the course of the last several years, at least 5 genetic defects have been shown to be associated with this group of immunodeficiencies.(1-3) These genetic defects include mutations that affect: -The costimulatory molecule, CD40LG, induced on activated T cells -The CD40LG receptor, CD40, expressed constitutively on B cells -Activation-induced cytidine deaminase (AID or AICDA), involved in somatic hypermutation (SHM) and isotype class-switching -Uracil DNA glycosylase (UNG), also involved in isotype class-switching and partially in SHM -NF-kappa B essential modulator (NEMO), also known as IKK gamma, which modulates NF-kappa B function(2,3) The mutations that occur in the CD40LG and CD40 genes are associated with X-linked hyper-IgM (type 1) and autosomal recessive hyper-IgM (type 3), respectively. Patients with mutations in either of these 2 genes are particularly prone to infections with opportunistic pathogens, such as Pneumocystis jiroveci, Cryptosporidium parvum, and Toxoplasma gondii.(4) All of the hyper-IgM syndromes (except those due to UNG defects and a hitherto undefined autosomal recessive [non-type 3] hyper-IgM) are associated with defects in isotype class-switching and SHM.(4) In the undefined autosomal recessive hyper-IgM there is no SHM defect, and in UNG deficiency there is biased SHM.(4) The impairment in isotype class-switching leads to the increased IgM levels with corresponding decrease in the "switched" immunoglobulins such as IgG, IgA, and even IgE. In the adult patient, hyper-IgM syndromes can overlap clinically with common variable immunodeficiency (CVID). However, patients with CD40LG (X-linked hyper-IgM; HIGM1) and CD40 (hyper-IgM type 3; HIGM3) mutations invariably present in infancy with upper and lower respiratory tract infections and opportunistic infections as previously described. HIGM1 is the most common of all the hyper-IgM syndromes described thus far, while HIGM3 is much rarer. Intermittent neutropenia is common in HIGM1 and has also been reported for HIGM3. Both diseases show significant decreases in class-switched memory (CD27+IgM-IgD-) B cells, corresponding to profound reductions in serum IgG and IgA levels. Peripheral T-cell subsets are normal, though in HIGM1 the number of CD45RO+ memory T cells is reduced. T-cell lymphocyte proliferative responses to mitogens are normal in both HIGM1 and HIGM3, while responses to specific antigen are abnormal in HIGM1 and normal in HIGM3. TBBS / T- and B-Cell Quantitation by Flow Cytometry and IABC / B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood evaluate isotype class-switching defects with identification of various memory B-cell subsets, including class-switched memory B cells. The other components of this panel include the CD40LG XHIM / X-linked Hyper IgM Syndrome, Blood, and CD40 / B-Cell CD40 Expression by Flow Cytometry, Blood, which is the CD40 assay for HIGM3. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. Natural Killer (NK)-cell counts, on the other hand, are constant throughout the day.(5) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(6,7,8) In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells.(6) It is generally accepted that lower CD4-T cell counts are seen in the morning compared to the evening(9) and during summer compared to winter.(10) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Diagnosis of hyper-IgM syndromes, specifically X-linked hyper-IgM (HIGM1) and autosomal recessive hyper-IgM type 3 (HIGM3) Evaluation of isotype class-switching defects

Interpretation: An interpretive report will be provided. The absence of CD40LG on activated T cells is consistent with X-linked hyper-IgM syndrome (HIGM1). The presence of CD40LG on activated T cells is not consistent with HIGM1. The presence of a positive and negative population for CD40LG is consistent with HIGM1 carrier status (mosaic). Negative CD40-muIg staining is consistent with HIGM1. Positive CD40-muIg staining is not consistent with HIGM1. Some patients (approximately 20%) show absent (negative) staining with the CD40-muIg antibody, while there is positive staining for surface CD40LG on activated T cells. This dichotomy is due to the presence of specific mutations in the CD40LG
gene that permit normal surface expression of the protein but abrogate function. Therefore, measurement of the receptor-ligand binding function using the chimeric CD40-muIg antibody improves the specificity of the assay, enabling identification of CD40LG-deficient patients who would be missed otherwise. The absence of CD40LG protein expression or CD40-muIg binding is considered confirmatory for HIGM1. Genetic testing is not necessary to confirm the diagnosis, but may be performed to identify the specific mutation involved. The absence of CD40 on B cells is consistent with autosomal recessive hyper-IgM type 3 (HIGM3). The presence of CD40 on B cells is not consistent with HIGM3. Reduced or absent class-switched memory B cells (CD27+IgM-IgD-) is consistent with a defect in isotype class-switching. Normal numbers of class-switched memory B cells indicates the lack of an isotype class-switching defect.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References:

HYOX 86213

Hyperoxaluria Panel, Urine

Clinical Information: Increased urinary oxalate frequently leads to renal stone formation and renal insufficiency. Identifying the cause of hyperoxaluria has important implications in therapy, management and prognosis. Hyperoxalurias are classified as primary and secondary. Primary hyperoxaluria is an inherited disorder of oxalate metabolism while secondary hyperoxaluria is an acquired condition resulting from either increased intake of dietary oxalate or altered intestinal oxalate absorption. Primary hyperoxalurias are classified into types 1, 2, and 3. Type 1 (PH1), an autosomal recessive deficiency of peroxisomal alanine: glyoxylate aminotransferase due to mutations in the AGXT gene, is characterized by increased urinary oxalic, glyoxylic, and glycolic acids. PH1 is the most common with manifestations that include deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and end-stage renal disease. Calcium oxalate deposits can be further deposited in other tissues such as the heart and eyes, and lead to a variety of additional symptoms. Age of onset is variable with a small percentage of patients presenting in the first year of life with failure to thrive, nephrocalcinosis, and metabolic acidosis. Approximately half of affected individuals show manifestations of PH1 in late childhood or early adolescence, and the remainder present in adulthood with recurrent renal stones. Some individuals with PH1 respond to supplementary pyridoxine therapy. Hyperoxaluria type 2 (PH 2) is due to a defect in GRHPR gene resulting in a deficiency of the enzyme hydroxypyruvate reductase. PH2 is autosomal recessive and identified by an increase in urinary oxalic, glyoxylic, and glycolic acids. Like PH1, PH2 is characterized by deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and end-stage renal disease. Most individuals have symptoms of PH2 during childhood, and it is thought that PH2 is less common than PH1. Hyperoxaluria type 3 (PH3), due to recessive mutations in HOGA1 (formerly DHDPSL), occurs in a small percentage of individuals with primary hyperoxaluria. HOGA1 encodes a mitochondrial 4-hydroxy-2-oxoglutarate aldolase that catalyzes the 4th step in the hydroxyproline pathway. PH3 is characterized biochemically by increased urinary excretion of oxalate and 4-hydroxy-2-oxoglutarate (HOG). As with PH types 1 and 2, PH type 3 is characterized by...
calcium-oxalate deposition in the kidneys and/or kidney stone formation. Most individuals with PH3 have early onset disease with recurrent kidney stones and urinary tract infections as common symptoms. End-stage renal disease is not a characteristic of PH3. Of note, individuals with heterozygous mutations in HOGA1 can have variable and intermittent elevations of urine oxalate. Secondary hyperoxalurias are due to hyperabsorption of oxalate (enteric hyperoxaluria); total parenteral nutrition in premature infants; ingestion of oxalate, ascorbic acid, or ethylene glycol; or pyridoxine deficiency, and may respond to appropriate therapy. A diagnostic workup in an individual with hyperoxaluria demonstrates increased concentration of oxalate in urinary metabolite screening. If glycolate, glycerate, or HOG is present, a primary hyperoxaluria is indicated. Additional analyses can include molecular testing for PH1 (AGXTG / Alanine:Glyoxylate Aminotransferase (AGXT) Mutation Analysis (G170R), Blood or AGXTZ / AGXT Gene, Full Gene Analysis), PH2 (GRHPZ / GRHPR Gene, Full Gene Analysis), or PH3 (HOGA1 testing not available at Mayo at this time).

**Useful For:** Distinguishing between primary and secondary hyperoxaluria Distinguishing between primary hyperoxaluria types 1, 2, and 3

**Interpretation:** Increased concentrations of oxalate and glycolate indicate type 1 hyperoxaluria. Increased concentrations of oxalate and glycerate indicate type 2 hyperoxaluria. Increased concentrations of oxalate and 4-hydroxy-2-oxoglutarate indicate type 3 hyperoxaluria. Increased concentrations of oxalate with normal concentrations of glycolate, glycerate, and 4-hydroxy-2-oxoglutarate indicate secondary hyperoxaluria.

**Reference Values:**

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**FHYPP 57739**

**Hypersensitivity Pneumonitis Extended Panel (Farmer's Lung Panel)**

**Reference Values:**

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<th></th>
<th>A. fumigatus #1 Ab, Precipitin</th>
<th>A. fumigatus #6 Ab, Precipitin</th>
<th>A. pullulans Ab, Precipitin</th>
<th>Pigeon Serum, Ab, Precipitin</th>
<th>M. faeni Ab, Precipitin</th>
<th>T. vulgaris #1 Ab, Precipitin</th>
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</table>

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1086
A. flavus Ab, Precipitin
None Detected

A. fumigatus #2 Ab, Precipitin
None Detected

A. fumigatus #3 Ab, Precipitin
None Detected

S. viridis Ab, Precipitin
None Detected

T. candidus Ab, Precipitin
None Detected

T. sacchari Ab, Precipitin
None Detected

Allergen, Animal, Feather Mix IgE kU/L
Negative

Allergen, Food, Beef IgE kU/L

Allergen, Food, Pork IgE kU/L

Allergen, Fungi/Mold, Phoma betae IgE kU/L

Allergen, Interp, Immunocap Score IgE

See Reference, Interval: Allergen, Interpretation A. Pullulans Ab, Precipitin:
Testing includes antibodies directed at Aureobasidium pullulans, Aspergillus flavus,
Aspergillus fumigatus #1, Aspergillus fumigatus #2, Aspergillus fumigatus #3,
Aspergillus fumigatus #6, Micropolyspora faeni, Saccharomonomospora viridis,
Thermoactinomyces candidus, Thermoactinomyces vulgaris #1, and
Thermoactinomyces vulgaris #1, and Thermoactinomyces sacchari. Allergen, Interp,
Immunocap Score IgE: Reference Interval: Allergen, Interpretation Less than 0.10 kU/L
No significant level detected 0.10-0.34 kU/L
Clinical relevance undetermined 0.35-0.70
kU/L Low 0.71-3.50 kU/L Moderate
3.51-17.50 kU/L High 17.51 or Greater kU/L
Very High Allergen results of 0.10-0.34 kU/L
are intended for specialist use as the clinical relevance is undetermined. Even though
increasing ranges are reflective of increasing concentrations of allergen-specific IgE, these
concentrations may not correlate with the degree of clinical response of skin testing
results when challenged with a specific allergen. The correlation of allergy laboratory
results with clinical history and in vivo reactivity to specific allergens is essential. A
negative test may not rule out clinical allergy or even anaphylaxis.
Hypersensitivity Pneumonitis IgG Antibodies, Serum

Clinical Information: Hypersensitivity pneumonitis (HP) is a heterogeneous disease caused by exposure to organic dust antigens, animal proteins, chemicals, medications, or microorganisms (e.g., Thermoactinomyces vulgaris, Micropolyspora faeni, Aspergillus fumigatus). The immunopathogenesis of disease is not known; but, several immunologic mechanisms may play a role in producing alveolitis, including cellular immunity mediated by CD4 and CD8 T lymphocytes, immune-complex mediated inflammation, complement activation or activation of alveolar macrophages. HP is suspected clinically in patients who present with intermittent or progressive pulmonary symptoms and interstitial lung disease. The diagnosis is established by compatible clinical and radiographic findings, pulmonary function tests, and demonstration of specific antibodies to organic antigens known to cause the disease.

Useful For: Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni

Interpretation: Elevated concentrations of IgG antibodies to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

Reference Values:
- Aspergillus fumigatus, IgG ANTIBODIES
  - <4 years: not established
  - > or =4 years: < or =102 mg/L
- Micropolyspora faeni, IgG ANTIBODIES
  - 0-12 years: < or =4.9 mg/L
  - 13-18 years: < or =9.1 mg/L
  - >18 years: < or =13.2 mg/L
- Thermoactinomyces vulgaris, IgG ANTIBODIES
  - 0-12 years: < or =6.6 mg/L
  - 13-18 years: < or =11.0 mg/L
  - >18 years: < or =23.9 mg/L

Clinical References:

Hypertrophic Cardiomyopathy Multi-Gene Panel, Blood

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC). The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The pathological hallmark of HCM is "myocyte disarray" where there is a loss of parallel alignment of myocytes in the heart wall. HCM is most often caused by...
genes encoding the cardiac sarcomere, the functional contractile unit of the heart muscle. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can cause life-threatening arrhythmias, which increase the risk of sudden cardiac death. The incidence of HCM in the general population is approximately 1 in 500. Inheritance is autosomal dominant, but compound heterozygosity (biallelic variants in the same gene) and digenic inheritance (variants in 2 different HCM-associated genes) do occur. The MYBPC3, MYL2, MYL3, MYH7, ACTC, TPM1, TNNI3, TNNT2, and CAV3 genes are involved in formation and regulation of the cardiac sarcomere, and account for the majority of variants in HCM. Left ventricular hypertrophy can also be caused by metabolic or storage disorders such as Fabry disease (GLA gene), Danon disease (LAMP2 gene), and Wolf-Parkinson-White syndrome associated with variants in the PRKAG2 gene. The TTR gene causes familial transthyretin amyloidosis, which is characterized by buildup of amyloid protein that affects the peripheral and autonomic nervous system. Other nonneuropathic changes may also be involved, including cardiomyopathy. See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Hypertrophic Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKRD1 Ankyrin repeat domain-containing protein 3 AD HCM, DCM, CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tateyama-type distal myopathy, rippling muscle disease CSRP3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, Neurogenic Scapuloperoneal Syndrome Kaeser Type, LGMD GLA Galactosidase, alpha X-linked Fabry disease LAMP2 Lysosome-associated membrane protein 2 X-linked Danon disease MYBPC3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light chain 2, regulatory, cardiac, slow AD HCM MYL3 Myosin, light chain 3, alkali, ventricular, skeletal, slow AD, AR HCM MYLK2 Myosin light chain kinase 2 AD HCM MYOZ2 Myozenin 2 AD HCM NEXN Nexilin AD HCM, DCM, PLN Phospholamban AD HCM, DCM, PRKAG2 Protein kinase, amp-activated, noncatalytic, gamma2 AD HCM, Wolff-Parkinson-White syndrome RAF1 V-RAF-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome TCAP Titin-cap (telethonin) AD, AR HCM, DCM, LGMD TNNC1 Troponin C, slow AD HCM, DCM, TNNI3 Troponin I, cardiac AD, AR DCM, HCM, RCM TNNT2 Troponin T2, cardiac AD HCM, DCM, RCM, LVNC TPM1 Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Congenital heart defects (CHD), long QT syndrome (LQTS), limb-girdle muscular dystrophy (LGMD), autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hypertrophic cardiomyopathy (HCM) Establishing a diagnosis of a hereditary HCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identification of a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


HYPOG 82439

Hypoglycemic Agent Screen, Serum

Clinical Information: The metabolic and hormonal profiles of insulinoma and sulfonylurea-induced hypoglycemia are identical. Therefore, in the evaluation of the hypoglycemic patient, the possible use of oral hypoglycemic agents as the cause for low blood glucose and elevated plasma insulin must be considered. Absence of hypoglycemic drugs in blood serum during an episode of low blood glucose should be demonstrated before considering pancreatic exploration for suspected insulinoma.

Useful For: Evaluation of suspected insulinoma characterized by hypoglycemia and increased plasma insulin concentration. Detecting drugs that stimulate insulin secretion If hypoglycemia is the result of 1 of these drugs, the test will detect the drug at physiologically significant concentrations in serum during an episode of hypoglycemia. Drugs detected by this procedure are: -The first-generation sulfonylureas-acetohexamide, chlorpropamide, tolazamide, and tolbutamide -The second-generation sulfonylureas--glimepiride, glipizide, and glyburide -The meglitinide-repaglinide Drugs designed to make tissues more sensitive to insulin that do not induce hypoglycemia, such as pioglitazone, rosiglitazone, and troglitazone (recently withdrawn from the United States market) are not included in this screen test. Drugs that lower blood glucose through mechanisms not related to stimulation of insulin secretion, such as acarbose, metformin, and miglitol are not included in this screen test.

Interpretation: Use of hypoglycemic agents outside of the context of treatment of type 2 diabetes is likely to cause hypoglycemia associated with elevated plasma insulin. Patients presenting with hypoglycemia due to ingestion of a first-, second-, or third-generation hypoglycemic agent will have drug present in serum greater than the minimum effective concentration (see Reference Values). Presence of drug indicates that the patient has recently ingested a hypoglycemic agent.

Reference Values:
ACETOHEXAMIDE
Negative: <1,000 ng/mL

CHLORPROPAMIDE
Negative: <1,000 ng/mL

TOLAZAMIDE
Negative: <20 ng/mL

TOLBUTAMIDE
Negative: <50 ng/mL

GLIMEPIRIDE
Negative: <20 ng/mL

GLIPIZIDE
Negative: <3 ng/mL

GLYBURIDE
Negative: <3 ng/mL
REPAGLINIDE
Negative: <3 ng/mL
Note: The report indicates a specific drug is positive if that drug is detected at a concentration greater than the sensitivity limit. The test sensitivity limit listed for each drug is lower than the concentration that will cause increased insulin and decreased glucose.


HIF2A
Hypoxia-Inducible Factor Alpha (EPAS1/HIF2A) Gene, Exons 9 and 12 Sequencing

Clinical Information: Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

Useful For: Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

Interpretation: Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

Reference Values: Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

Clinical References:

FIBUP
Ibuprofen (Motrin, Advil, Nuprin), serum

Reference Values:
Reference Range: 10.0 - 50.0 ug/mL

LCHB
Id, Histoplasma/Blastomyces PCR (Bill Only)

Reference Values:
This test is for billing purposes only. This is not an orderable test.

RMALD
Ident by MALDI-TOF Mass Spec (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LCCI
Ident Rapid PCR Coccidioides (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PCRID
Identification by PCR (Bill Only)
**IDH1/2, Mutation Analysis**

**Clinical Information:** Adult World Health Organization (WHO) grade II and III astrocytomas, oligodendroglialomas and oligoastrocytomas, and secondary glioblastomas (GBM) have been shown to harbor IDH1 and IDH2 mutations. These missense mutations most frequently involve the arginine amino acid at IDH1 position 132 (R132) and at IDH2 position 172 (R172). The most frequent IDH1 amino acid alteration accounting for over 90% mutations is R132H, in addition to R132C, R132S, R132G, R132L, and R132V. For IDH2, R172K, R172G, R172M, and R172W mutations have also been reported. IDH1 proteins are nicotinamide adenine dinucleotide phosphate (NADP)-dependent isocitrate dehydrogenases that catalyze the oxidative decarboxylation of isocitrate to produce alpha-ketoglutarate. IDH1 and IDH2 mutations appear to be an early event in the development of these tumors and impair the enzyme activity, resulting in loss of the ability to catalyse conversion of isocitrate to alpha-ketoglutarate. However, the enzyme acquires a neomorphic activity and is able to catalyze the NADPH-reduction of alpha-ketoglutarate to R(-)-2-hydroxyglutarate (2HG). These mutations appear to have prognostic significance with increased overall survival and have been found to be associated with a younger age among adult diffuse astrocytomas, WHO grade III astrocytomas, and GBM patients. Of note, IDH1 mutations are only rarely reported among pilocytic astrocytomas, primary GBM, supratentorial primitive neuroectodermal tumors, and pleomorphic xanthoastrocytomas. IDH1 and IDH2 mutations are absent in pediatric diffuse astrocytomas, ependymomas, medulloblastomas, primitive neuroectodermal tumors, and dysembryoblastic tumors.

**Useful For:** Supporting a diagnosis of grade II or III astrocytoma, oligodendroglioma, oligoastrocytoma, or secondary glioblastoma. Stratifying prognosis of gliomas

**Interpretation:** The presence of an IDH1 or IDH2 mutation supports a diagnosis of grade II or III astrocytoma, oligodendroglioma, oligoastrocytoma, or secondary glioblastoma (GBM) in the context of other corroborating pathologic features. IDH1 codon 132 and IDH2 codon 172 mutations have been identified in more than 70% of brain tumors diagnosed as grade II and III astrocytoma, oligodendroglioma, oligoastrocytoma, and secondary GBM. These mutations are rarely found in other brain tumors and nonbrain tumors. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided. A negative result does not exclude the presence of a brain tumor.

**Reference Values:**
An interpretative report will be provided.

Iduronate-2-Sulfatase, Blood Spot

Clinical Information: The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Accumulation of GAGs (previously called mucopolysaccharides) in the lysosomes interferes with normal functioning of cells, tissues, and organs. Mucopolysaccharidosis II (MPS II, Hunter syndrome) is an X-linked lysosomal storage disorder caused by the deficiency of iduronate sulfatase (IDS) enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms are widely variable ranging from severe disease to an attenuated form, which generally has a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, Hunter disease occurs almost exclusively in males with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. A diagnostic workup in an individual with MPS II typically demonstrates elevated levels of urinary glycosaminoglycans and increased amounts of both dermatan and heparan sulfate. Reduced or absent activity of IDS can confirm a diagnosis of MPS II; however, enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in female relatives. Currently, no clear genotype-phenotype correlations have been established.

Useful For: Diagnosis of mucopolysaccharidosis II (MPS II, Hunter syndrome) using dried blood spot specimens

Interpretation: Specimens with results <1.5 nmol/h/mL in properly submitted specimens are consistent with iduronate-2-sulfatase deficiency (mucopolysaccharidosis II: MPS II). If clinically indicated, consider further confirmation by molecular genetic analysis of the IDS gene. Please note that this enzyme’s activity can also be reduced in multiple sulfatase deficiency (MSD; OMIM #272200). If clinically indicated, consider biochemical genetic testing of other sulfatases or molecular genetic testing of the SUMF1 gene to exclude MSD. Normal results (> or =1.5 nmol/h/mL) are not consistent with iduronate-2-sulfatase deficiency.

Reference Values:
> or =1.5 nmol/h/mL


Iduronate-2-sulfatase, Whole Blood

Clinical Information: The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Accumulation of GAGs (previously called mucopolysaccharides) in the lysosomes interferes with normal functioning of cells, tissues, and organs. Mucopolysaccharidosis II (MPS II, Hunter syndrome) is an X-linked lysosomal storage disorder caused by the deficiency of iduronate sulfatase (IDS) enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms are widely variable ranging from severe disease to an attenuated form, which generally has a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, Hunter disease occurs almost exclusively in males with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS II typically demonstrates elevated levels of urinary glycosaminoglycans and...
increased amounts of both dermatan and heparan sulfate. Reduced or absent activity of IDS can confirm a diagnosis of MPS II; however, enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in female relatives. Currently, no clear genotype-phenotype correlations have been established.

**Useful For:** Diagnosis of mucopolysaccharidosis II (MPS II, Hunter syndrome)

**Interpretation:** Specimens with results <1.5 nmol/h/mL in properly submitted specimens are consistent with iduronate-2-sulfatase deficiency (mucopolysaccharidosis II: MPS II). If clinically indicated, consider further confirmation by molecular genetic analysis of the IDS gene. Please note that this enzyme's activity can also be reduced in multiple sulfatase deficiency (MSD; OMIM #272200). If clinically indicated, consider biochemical genetic testing of other sulfatases or molecular genetic testing of the SUMF1 gene to exclude MSD. Normal results (> or =1.5 nmol/h/mL) are not consistent with iduronate-2-sulfatase deficiency.

**Reference Values:**
> or =1.5 nmol/h/mL

**Clinical References:**

**IGAS Subclasses, Serum**

**Clinical Information:** IgA, the predominant immunoglobulin secreted at mucosal surfaces, consists of 2 subclasses, IgA1 and IgA2. IgA1 is the major (approximately 80%) subclass in serum. IgA2 is the major subclass in secretions such as milk. Although IgA deficiency is a common defect (1 in 700), it is usually asymptomatic. IgA deficiency with or without IgG subclass deficiency, however, can lead to recurrent pulmonary and gastrointestinal infections. Some infections (eg, recurrent sinopulmonary infections with Haemophilus influenzae) may be related to a deficiency of IgA2 in the presence of normal total IgA concentrations. Paradoxically, bacterial infections may also cause IgA deficiency. For example, IgA1 (but not IgA2) can be cleaved and inactivated by certain bacteria, thus depleting the majority of the IgA. In the presence of a concurrent IgA2 deficiency, infection by these organisms results in an apparent IgA deficiency. IgA deficiency is 1 cause of anaphylactic transfusion reactions. In these situations, IgA-deficient patients produce anti-IgA antibodies that react with IgA present in the transfusion product. While transfusion reactions typically occur in patients who have no detectable levels of IgA, they can occur in patients with measurable IgA. In these situations, the complete deficiency of 1 of the IgA subclasses may be the cause of the transfusion reactions.

**Useful For:** Investigation of immune deficiency due to IgA2 deficiency Evaluating patients with anaphylactic transfusion reactions

**Interpretation:** Low concentrations of IgA2 with normal IgA1 levels suggest an IgA2 deficiency. Elevated concentrations of IgA2 with normal or low amounts of IgA1 suggest a clonal plasma cell proliferative disorder secreting a monoclonal IgA2. Increased total IgA levels also may be seen in benign disorders (eg, infection, inflammation, allergy), hyper IgD syndrome with periodic fever and monoclonal gammopathies (eg, myeloma, monoclonal gammopathies of undetermined significance [MGUS]).

**Reference Values:**

<table>
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<th>IgA</th>
<th>0-&lt;5 months: 7-37 mg/dL</th>
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<tr>
<td></td>
<td>5-&lt;9 months: 16-50 mg/dL</td>
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<td></td>
<td>9-&lt;15 months: 27-66 mg/dL</td>
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<tr>
<td></td>
<td>15-&lt;24 months: 36-79 mg/dL</td>
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<tr>
<td></td>
<td>2-&lt;4 years: 27-246 mg/dL</td>
</tr>
<tr>
<td></td>
<td>4-&lt;7 years: 29-256 mg/dL</td>
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7-<10 years: 34-274 mg/dL  
10-<13 years: 42-295 mg/dL  
13-<16 years: 52-319 mg/dL  
16-<18 years: 60-337 mg/dL  
> or =18 years: 61-356 mg/dL

IgA1  
0-<5 months: 10-34 mg/dL  
5-<9 months: 14-41 mg/dL  
9-<15 months: 20-50 mg/dL  
15-<24 months: 24-58 mg/dL  
2-<4 years: 16-162 mg/dL  
4-<7 years: 17-187 mg/dL  
7-<10 years: 21-221 mg/dL  
10-<13 years: 27-250 mg/dL  
13-<16 years: 36-275 mg/dL  
16-<18 years: 44-289 mg/dL  
> or =18 years: 50-314 mg/dL

IgA2  
0-<5 months: 0.4-5.5 mg/dL  
5-<9 months: 1.5-6.2 mg/dL  
9-<15 months: 2.8-7.0 mg/dL  
15-<24 months: 3.9-7.7 mg/dL  
2-<4 years: 1.3-31.1 mg/dL  
4-<7 years: 1.1-39.1 mg/dL  
7-<10 years: 1.4-48.0 mg/dL  
10-<13 years: 2.6-53.4 mg/dL  
13-<16 years: 4.7-55.1 mg/dL  
16-<18 years: 6.6-54.3 mg/dL  
> or =18 years: 9.7-156.0 mg/dL


### FIGBP 57131

**IGF Binding Protein-1 (IGFBP-1)**

**Reference Values:**

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<th>Units: ng/mL</th>
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<tbody>
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<td>Age</td>
</tr>
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<tr>
<td>Fasting</td>
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<td>Random</td>
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<td>Adults</td>
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Current as of July 8, 2016 11:28 am CDT  
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  
Page 1095
IgG Subclasses, Serum

Clinical Information: The most abundant immunoglobulin in human serum is immunoglobulin G (IgG) (approximately 80% of the total). IgG protein is comprised of molecules of 4 subclasses designated IgG1 through IgG4. Each subclass contains molecules with a structurally unique gamma heavy chain. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Molecules of different IgG subclasses have somewhat different biologic properties (eg, complement fixing ability and binding to phagocytic cells), which are determined by structural differences in gamma heavy chains. Clinical interest in IgG subclasses concerns potential immunodeficiencies (eg, subclass deficiencies) and IgG4-related diseases (eg, IgG4 elevations). The IgG subclass assay (IGGS / IgG Subclasses, Serum) is best for deficiency testing, and the IgG4 assay (IGGS4 / Immunoglobulin Subclass IgG4, Serum) is best for IgG4-related disease testing. Diminished concentrations of IgG subclass proteins may occur in the context of hypogammaglobulinemia (eg, in common variable immunodeficiency where all immunoglobulin classes are generally affected) or deficiencies may be selective, usually involving IgG2. Deficiency of IgG1 usually occurs in patients with severe immunoglobulin deficiency involving other IgG subclasses. Deficiency of IgG2 is more heterogeneous and can occur as an isolated deficiency or in combination with deficiency of immunoglobulin A (IgA), or of IgA and other IgG subclasses. Most patients with IgG2 deficiency present with recurrent infections, usually sinusitis, otitis, or pulmonary infections. Children with deficiency of IgG2 often have deficient antibody responses to polysaccharide antigens including bacterial antigens associated with Haemophilus influenzae type B and Streptococcus pneumoniae. Isolated deficiencies of IgG3 or IgG4 occur rarely, and the clinical significance of these findings is not clear.

Useful For: A second-order test for evaluating patients with clinical signs and symptoms of humoral immunodeficiency or combined immunodeficiency (cellular and humoral) Testing for immunoglobulin G (IgG) subclass levels may be indicated in patients with clinical evidence of a possible immunodeficiency with hypogammaglobulinemic patients or normal concentrations of total serum IgG.

Interpretation: Diminished concentrations of all immunoglobulin G (IgG) subclasses are found in common variable immunodeficiency, combined immunodeficiency, ataxia telangiectasia, and other primary and acquired immunodeficiency diseases. A diminished concentration of IgG2 protein may be clinically significant in the context of recurrent sinopulmonary infection and may occur with or without concomitant immunoglobulin A deficiency. Slightly diminished concentrations of 1 or more IgG subclass proteins are not uncommon, and usually have little clinical significance. Conversely, some individuals with deficient specific antibody responses to polysaccharide antigens may have normal serum levels of IgG subclasses.

Reference Values:

TOTAL IgG
0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL
16-<18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

IgG1
0-<5 months: 56-215 mg/dL
5-<9 months: 102-369 mg/dL
9-<15 months: 160-562 mg/dL
15-<24 months: 209-724 mg/dL
2-<4 years: 158-721 mg/dL
### IgG

<table>
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<th>Value Range</th>
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<tbody>
<tr>
<td>0-&lt;5 months</td>
<td>&lt; or =82 mg/dL</td>
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<tr>
<td>13-&lt;16 years</td>
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<td>16-&lt;18 years</td>
<td>98-486 mg/dL</td>
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<td>&gt; or =18 years</td>
<td>171-632 mg/dL</td>
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### IgG3

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<td>11.9-74.0 mg/dL</td>
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<td>9-&lt;15 months</td>
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<td>2-&lt;4 years</td>
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### IgG4

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<td>2-&lt;4 years</td>
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<td>4-&lt;7 years</td>
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<td>10-&lt;13 years</td>
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<td>0.3-111.0 mg/dL</td>
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<tr>
<td>&gt; or =18 years</td>
<td>2.4-121.0 mg/dL</td>
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**Clinical Information:**

Elevation of IgG levels in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) (multiple sclerosis, neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to local (CNS) synthesis of IgG. The two most commonly used diagnostic laboratory tests for multiple sclerosis are CSF index and oligoclonal banding. The CSF index is the CSF IgG to CSF albumin ratio compared to the...
serum IgG to serum albumin ratio. The CSF index is therefore an indicator of the relative amount of CSF IgG compared to serum and any increase in the index is a reflection of IgG production in the central nervous system. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases.

**Useful For:** The cerebrospinal fluid (CSF) index is useful in the diagnosis of individuals with multiple sclerosis. In the absence of a paired CSF and serum specimen, the CSF IgG/albumin ratio can be assessed. The index is independent of the activity of the demyelinating process.

**Interpretation:** Cerebrospinal fluid IgG index is positive (elevated) in approximately 80% of patients with multiple sclerosis.

**Reference Values:**
- CSF IgG: 0.0-8.1 mg/dL
- CSF albumin: 0.0-27.0 mg/dL
- CSF IgG/albumin: 0.00-0.21

**Clinical References:**

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**FG4FI**

57851

**IgG4 Food Panel I**

**Reference Values:**
- Alpha Lactalbumin IgG4 <0.15
- Beef IgG4 <0.15
- Casein IgG4 <0.15
- Chicken IgG4 <0.15
- Corn IgG4 <0.15
- Egg Whole IgG4 <0.15
- Milk Cow IgG4 <0.15
- Potato White IgG4 <0.15
- Soybean IgG4 <0.15
- Wheat IgG4 <0.15

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question.

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**FGFP2**

57904

**IgG4 Food Panel II**

**Reference Values:**
- Banana IgG4
- Chocolate/Cacao IgG4
- Milk Goat IgG4
- Oat IgG4
Orange IgG4
Peanut IgG4
Pork IgG4
Rice IgG4
Tomato IgG4

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question.

**FG4FP 57591**

**IgG4 Food Panel VIII**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**
- Corn IgG4 <0.15 mcg/mL
- Egg White IgG4 <0.15 mcg/mL
- Milk Cow IgG4 <0.15 mcg/mL
- Peanut IgG4 <0.15 mcg/mL
- Soybean IgG4 <0.15 mcg/mL
- Wheat IgG4 <0.15 mcg/mL

This test should only be ordered by physicians who recognize the limitations of the test.

**BCLL 89008**

**IGH Somatic Hypermutation Analysis, B-Cell Chronic Lymphocytic Leukemia (B-CLL)**

**Clinical Information:** During early B-cell development, IGH genes are assembled from multiple polymorphic gene segments that undergo rearrangements and selection, generating VDJ combinations that are unique in both length and sequence for each B cell. In addition, new acquired(somatic) point mutations are introduced into the variable (V) regions of mature B cells during the germinal center reaction in lymph nodes, and this process is called somatic hypermutation (SHM). Since chronic lymphocytic leukemia (CLL) leukemias originate from the malignant transformation of single lymphoid cells, each daughter cell shares 1 or (sometimes) more unique "clonal" antigen receptor gene rearrangements, which are cell and therefore tumor specific (ie, a tumor cell "fingerprint"). Clonal IGHV gene hypermutation status provides important prognostic information for patients with CLL and small lymphocytic lymphoma (SLL). The presence of IGH somatic hypermutation (SHM) is defined as greater or equal to 2% difference from the germline VH gene sequence identity (mutated), whereas less than 2% difference is considered no somatic hypermutation (umutated). The status of somatic hypermutation has clear influence on the median survival of CLL patients. Hypermutation of the IGH variable region is strongly predictive of a good prognosis while lack of mutation predicts a poorer prognosis. Although the
determination of mutation status can be accomplished by PCR followed by Sanger sequencing, this approach only allows for analysis of single samples at a time. Next-generation sequencing (NGS) technology (eg, using the Illumina MiSeq platform) represents a significant improvement over existing Sanger assays by allowing for batch sample analysis and simultaneous identification of clonal IGH rearrangement, the tumor-specific rearrangement sequence, and determination of somatic mutation percent.

**Useful For:** Providing prognostic information in patients with newly diagnosed B-cell chronic lymphocytic leukemia

**Interpretation:** The presence or absence of somatic hypermutation in the immunoglobulin heavy chain gene (IGH) variable (V) region DNA will be reported. A mutation frequency of 2% or greater will be reported as mutated. Both the percent mutation and the V region allele identified in the rearrangement will be included in the report. B-cell chronic lymphocytic leukemia (B-CLL) lacking somatic hypermutation of the IGHV region (unmutated) is associated with a significantly worse prognosis than B-CLL containing somatic hypermutation of the IGHV region (mutated).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**PNS1**
IHC Initial Single Antibody Stain (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MBS1**
IHC Initial Single Antibody Stain (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This test is not an orderable test.

**MBS2**
IHC, Each Additional Antibody Stain (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This test is not an orderable test.

**PNS2**
IHC, Each Additional Antibody Stain (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
Clinical Information: Myeloid neoplasms are primary disorders of the bone marrow cells. These malignancies encompass several entities with extremely varied clinical courses, including acute myeloid leukemias (AML), chronic myeloproliferative disorders (CMPD), and myelodysplastic syndromes. The underlying genetic mechanisms associated with these malignancies are varied and only a portion of the genetic abnormalities have targeted therapies clinically available. One group of genes, including ABL1 (Abelson murine leukemia viral oncogene homolog 1), ABL2 (Abelson murine leukemia viral oncogene homolog 2), PDGFRA (platelet-derived growth factor receptor, alpha), and PDGFRB (platelet-derived growth factor receptor, beta) can be inappropriately activated via various genetic mechanisms and result in overexpression of their tyrosine kinase activity. Tyrosine kinase activity plays an important role in cellular signaling, division, and differentiation; overexpression may cause some cancers. The myeloid malignancies associated with these aberrantly expressed genes include AML, chronic myelogenous leukemia (CML), hypereosinophilic syndrome/systemic mast cell disease (HES/SMCD), and atypical CMPD. These translocations can also be seen in lymphoid neoplasms, including acute lymphoblastic leukemia (ALL) and lymphomas, and they can also possess a varied genetic etiology. Several clinical studies have demonstrated that the malignancies displaying overexpression of these genes are responsive to imatinib mesylate, a drug that specifically targets these genes.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with acute leukemia or other myeloid malignancies Tracking known chromosome abnormalities and response to therapy in patients with myeloid malignancies

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.


Imipramine and Desipramine, Serum

Clinical Information: Imipramine and its metabolite desipramine are tricyclic antidepressants used to treat endogenous depression requiring 1 to 3 weeks of treatment before therapeutic effectiveness becomes apparent. Desipramine is used for treatment of endogenous depression when the patient needs a drug with significant stimulatory side effects. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Imipramine The optimal dosage of imipramine yields trough (just before the next dose) blood levels of imipramine and desipramine combined from 175 to 300 ng/mL. If desipramine is given, no imipramine should be detected and the therapeutic concentration for desipramine alone is 100 to 300 ng/mL. Toxicity associated with imipramine is characterized by QRS widening leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations, or at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 300 ng/mL. Desipramine Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects; dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations in excess of 300 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 300...
Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

Interpretation: Most individuals display optimal response to imipramine when combined serum levels of imipramine and desipramine are between 175 and 300 ng/mL. Risk of toxicity is increased with levels $>$ or $\leq$300 ng/mL. Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Risk of toxicity is increased with desipramine levels $>$ or $\leq$300 ng/mL. Some individuals may respond well outside of these ranges, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Therapeutic ranges are based on specimen drawn at trough (ie, immediately before the next dose).

Reference Values:
IMIPRAMINE AND DESIPRAMINE
Total therapeutic concentration: 175-300 ng/mL

DESIPRAMINE ONLY
Therapeutic concentration: 100-300 ng/mL
Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


**IMFXO 32436**

**Immunofixation Only, Serum**

**Clinical Information:** Monoclonal gammopathies indicate a clonal expansion of plasma cells or mature B lymphocytes. The monoclonal gammapathies include diseases such as multiple myeloma, Waldenstrom’s macroglobulinemia, lymphoproliferative disease, primary systemic amyloidosis, light-chain deposition disease, as well as the premalignant disorders of smoldering myeloma and monoclonal gammapathy of undetermined significance (MGUS). Monoclonal gammapathy patients may have a relatively small monoclonal protein abnormality or a large quantifiable peak (M-spike) on serum or urine protein electrophoresis. Abnormalities detected on serum protein electrophoresis (SPEP) should be immunotyped to confirm and characterize the monoclonal protein. Immunotyping of monoclonal proteins is usually done by immunofixation electrophoresis (IFE) and identifies the monoclonal immunoglobulin heavy-chain (gamma, alpha, mu, delta, or epsilon) and/or light-chain type (kappa or lambda). It is generally recommended that both SPEP and IFE be used as a screening panel. Because IFE is more sensitive than SPEP, IFE is not only recommended as part of the initial screening process but also for confirmation of complete response to therapy.

Useful For: Identification of monoclonal immunoglobulin heavy and light chains Documentation of complete response to therapy

Interpretation: Immunofixation impression comments are made based on visual interpretation of gels.

Reference Values:
No monoclonal protein detected

Immunofixation, CSF

Reference Values:
Reference Range: No monoclonal proteins added.

Immunoglobulin A (IgA), Serum

Clinical Information: The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 15% is immunoglobulin A (IgA). Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgA characterize multiple myeloma. Decreased immunoglobulin levels are found in patients with congenital deficiencies. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet. To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Detection or monitoring of monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin A may occur in monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL


Immunoglobulin D (IgD), Serum
**Clinical Information:** Antibodies or immunoglobulins (Ig) are formed by plasma cells as a humoral immune response to antigens. The first antibodies formed after antigen stimulation are of the IgM class, followed later by IgG and also IgA antibodies. IgD normally occurs in serum in trace amounts. Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic diseases (chronic hepatitis, liver cirrhosis), acute and chronic infections, autoimmune diseases, as well as in the cord blood of neonates with intrauterine and perinatal infections. Increases in serum immunoglobulin concentration are seen in monoclonal gammapathies such as multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis, and monoclonal gammopathy of undetermined significance. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies including advanced monoclonal gammapathies, lymphatic leukemia, and advanced malignant tumors.

**Useful For:** Quantitative determination of the immunoglobulins can provide important information on the humoral immune status. Changes in IgD concentration are used as a marker of changes in the size of the clone of monoclonal IgD plasma cells.

**Interpretation:** The physiologic significance of serum IgD concentration is unclear and in many normal persons serum IgD is undetectable. Increased concentrations may be due to polyclonal (reactive) or monoclonal plasma cell proliferative processes. A monoclonal IgD protein is present in 1% of patients with myeloma. Monoclonal IgD proteins are often in low concentrations and do not have a quantifiable M-peak on serum protein electrophoresis. However, the presence of an IgD monoclonal protein is almost always indicative of a malignant plasma cell disorder such as multiple myeloma or primary amyloidosis.

**Reference Values:**

< or =10 mg/dL

**Clinical References:**

**Immunoglobulin E (IgE), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE are generally thought of in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease, except for allergic bronchopulmonary aspergillosis (ABPA). ABPA is a hypersensitivity reaction against the fungi Aspergillus that occurs most frequently in patients with asthma or cystic fibrosis. An elevation of total IgE is part of the diagnostic criteria for ABPA, although the specific diagnostic concentration is dependent on certain patient characteristics. For patients with an established diagnosis of allergic disease, measurement of total IgE is necessary for identification of candidates for omalizumab (anti-IgE) therapy, and for determination of proper dosing. In addition to specific patient demographics and clinical presentations, candidates for omalizumab must have total IgE concentrations between 30 and
**Useful For:** Evaluation of patients with suspected diseases associated with elevations in total immunoglobulin E (IgE), including allergic disease, primary immunodeficiencies, infections, malignancies, or other inflammatory diseases. Diagnostic evaluation of patients with suspected allergic bronchopulmonary aspergillosis. Identification of candidates for omalizumab (anti-IgE) therapy.

**Interpretation:** Elevated concentrations of total immunoglobulin E (IgE) may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Elevated total IgE concentrations may be consistent with a diagnosis of allergic bronchopulmonary aspergillosis, provided other laboratory and clinical criteria are fulfilled. Total IgE concentrations between 30 to 700 KU/L may identify candidates for omalizumab therapy and may help to determine proper therapeutic dosing.

**Reference Values:**

Results Reported in kU/L.

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months</td>
<td>&lt; or =13</td>
</tr>
<tr>
<td>6-11 months</td>
<td>&lt; or =34</td>
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<tr>
<td>1 and 2 years</td>
<td>&lt; or =97</td>
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<tr>
<td>3 years</td>
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<tr>
<td>4-6 years</td>
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<td>7 and 8 years</td>
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<td>13-15 years</td>
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<tr>
<td>16 and 17 years</td>
<td>&lt; or =537</td>
</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
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</tbody>
</table>

**Clinical References:**


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**FLCP**

**Immunoglobulin Free Light Chains, Serum**

**Clinical Information:** The monoclonal gammapathies are characterized by a clonal expansion of plasma cells that secrete a monoclonal immunoglobulin (Ig). The monoclonal Ig secreted by these cells serves as a marker of the clonal proliferation and the quantitation of monoclonal protein can be used to monitor the disease course. The monoclonal gammapathies include multiple myeloma (MM), light chain multiple myeloma (LCMM), Waldenstrom macroglubulinemia (WM), nonsecretory myeloma (NSMM), smoldering multiple myeloma (SMM), monoclonal gammapathy of undetermined significance (MGUS), primary systemic amyloidosis (AL), and light chain deposition disease (LCDD). Monoclonal proteins are typically detected by serum protein electrophoresis (SPEP) and immunofixation (IF). However, the monoclonal light chain diseases (LCMM, AL, LCDD) and NSMM often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by SPEP. A sensitive nephelometric assay specific for kappa free light chain (FLC) and lambda free light chain (FLC) that doesn't recognize light chains bound to Ig heavy chains has recently been described. This automated, nephelometric assay is reported to be more sensitive than IF for detection of monoclonal FLC. In some patients with NSMM, AL, or LCDD the FLC assay provides a positive identification of a monoclonal serum light chain when the serum IF is negative. In addition, the quantitation of FLC has been correlated with disease activity in...
patients with NSMM and AL. See Laboratory Approach to the Diagnosis of Amyloidosis and Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Monitoring patients with monoclonal light chain diseases but no M-spike on protein electrophoresis

**Interpretation:** The specificity of this assay for detection of monoclonal light chains relies on the ratio of free kappa and lambda (K/L) light chains. Once an abnormal free light chain (FLC) K/L ratio has been demonstrated and a diagnosis has been made, the quantitation of the monoclonal light chain is useful for monitoring disease activity. Changes in FLC quantitation reflect changes in the size of the monoclonal plasma cell population. Our experience to date is limited, but changes of >25% or trending of multiple specimens are needed to conclude biological significance.

**Reference Values:**

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA FLC RATIO
0.26-1.65


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**Immunoglobulin G (IgG), Serum**

**Clinical Information:** The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is immunoglobulin G (IgG). Elevations of IgG may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgG characterize multiple myeloma. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detecting or monitoring of monoclonal gammopathies and immune deficiencies

**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin G may occur in monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

**Reference Values:**

0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL
16-<18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

**Clinical References:** 1. Webster ADB: Laboratory investigation of primary deficiency of the


**Immunoglobulin Gene Rearrangement, Blood**

**Clinical Information:** The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the nonrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no 1 clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

**Useful For:** Determining whether a B-cell or plasma cell population is polyclonal or monoclonal. Identifying neoplastic cells as having B-cell or plasma cell differentiation. Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to one from a previous neoplastic specimen.

**Interpretation:** An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

**Immunoglobulin Gene Rearrangement, Bone Marrow**

**Clinical Information:** The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B-cells develop, the segments are rearranged such that each mature B-cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the nonrearranged gene structures. Clonal expansion of any B-cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no 1 clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B-cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

**Useful For:** Determining whether a B-cell or plasma cell population is polyclonal or monoclonal. Identifying neoplastic cells as having B-cell or plasma cell differentiation. Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to one from a previous neoplastic specimen.
neoplasm by detecting an immunoglobulin gene rearrangement profile similar to 1 from a previous neoplastic specimen

**Interpretation:** An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

**Reference Values:**
An interpretive report will be provided.


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**BCGRV 31142**

**Immunoglobulin Gene Rearrangement, Varies**

**Clinical Information:** The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the nonrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

**Useful For:** Determining whether a B-cell or plasma cell population is polyclonal or monoclonal

Identifying neoplastic cells as having B-cell or plasma cell differentiation

Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to that from a previous neoplastic specimen

**Interpretation:** An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

**Reference Values:**
An interpretive report will be provided.


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**HLCA 61719**

**Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgA Kappa and IgA Lambda**

**Clinical Information:** Plasma cell proliferative diseases such as multiple myeloma are defined by the monoclonal expansion of bone marrow plasma cells. The abnormal proliferation of clonal cells in the bone marrow can be identified by a skewed ratio of cells synthesizing kappa or lambda immunoglobulin. In addition, the secreted monoclonal immunoglobulin can usually be identified in serum or urine by
protein electrophoresis and immunofixation electrophoresis. These electrophoretic procedures can show restricted immunoglobulin migration, characterize the heavy and/or light chains, and quantitate the monoclonal protein. Some monoclonal proteins, however, are difficult to identify and quantitate by electrophoretic assays. The serum concentration of monoclonal free light chains for example may not be high enough to be recognized or quantitated. Immunoassays that are specific for free light chains, as opposed to light chains bound to heavy chains, can quantitate kappa and lambda free light chains. An abnormal ratio of the free light chains can identify excess clonal plasma cell proliferation and the concentration of the monoclonal free light chain can be determined. Another example of proteins that are difficult to identify and quantitate are monoclonal proteins that are intact immunoglobulins (heavy and light chains) that migrate very broadly in the gamma fraction or migrate within the beta or alpha fractions. Immunoassays that are specific for heavy and light chain pairs (HLC) such as IgA kappa or IgA lambda can quantitate the individual HLC pairs and be used to identify abnormal ratios of the HLC pairs and to quantitate the monoclonal HLC pair.

**Useful For:** The quantitation of heavy and light chain pairs is useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses 2. Quantitating monoclonal IgA proteins that are difficult to quantitate on serum protein electrophoresis 3. Providing a more specific quantitation of the monoclonal protein than quantitating total IgA

**Interpretation:** An elevated IgA heavy and light chain (HLC) pairs ratio suggests a clonal proliferation of an IgA kappa clone of plasma cells. A low IgA HLC pair ratio suggests a clonal proliferation of an IgA lambda clone of plasma cells.

**Reference Values:**

**Total IgA**
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL

**IgA kappa:** 53-262 mg/dL

**IgA lambda:** 38-181 mg/dL

**AK/AL ratio:** 0.5300-2.52

**Clinical References:**
electrophoretic assays. The serum concentration of monoclonal free light chains for example may not be high enough to be recognized or quantitated. Immunoassays that are specific for free light chains, as opposed to light chains bound to heavy chains, can quantitate kappa and lambda free light chains. An abnormal ratio of the free light chains can identify excess clonal plasma cell proliferation and the concentration of the monoclonal free light chain can be determined. Another example of proteins that are difficult to identify and quantitate are monoclonal proteins that are intact immunoglobulins (heavy and light chains) that migrate very broadly in the gamma fraction or migrate within the beta or alpha fractions. Immunoassays that are specific for heavy and light chain pairs (HLC) such as IgG kappa or IgG lambda can quantitate the individual HLC pairs and be used to identify abnormal ratios of the HLC pairs and to quantitate the monoclonal HLC pair.

**Useful For:** The quantitation of heavy and light chain pairs is useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses 2. Quantitating monoclonal IgG proteins that are difficult to quantitate on serum protein electrophoresis 3. Providing a more specific quantitation of the monoclonal protein than quantitating total IgG

**Interpretation:** An elevated IgG heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgG kappa clone of plasma cells. A low IgG HLC pair ratio suggests a clonal proliferation of an IgG lambda clone of plasma cells.

**Reference Values:**

**Total IgG**
- 0-<5 months: 100-334 mg/dL
- 5-<9 months: 164-588 mg/dL
- 9-<15 months: 246-904 mg/dL
- 15-<24 months: 313-1,170 mg/dL
- 2-<4 years: 295-1,156 mg/dL
- 4-<7 years: 386-1,470 mg/dL
- 7-<10 years: 462-1,682 mg/dL
- 10-<13 years: 503-1,719 mg/dL
- 13-<16 years: 509-1,580 mg/dL
- 16-<18 years: 487-1,327 mg/dL
- > or =18 years: 767-1,590 mg/dL

**IgG kappa:** 434-1080 mg/dL
**IgG lambda:** 177-531 mg/dL
**GK/GL ratio:** 1.06-4.46

**Clinical References:**

**Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgM Kappa and IgM Lambda**

**Clinical Information:** Plasma cell proliferative diseases such as multiple myeloma are defined by the monoclonal expansion of bone marrow plasma cells. The abnormal proliferation of clonal cells in the bone marrow can be identified by a skewed ratio of cells synthesizing kappa or lambda immunoglobulin. In addition, the secreted monoclonal immunoglobulin can usually be identified in serum or urine by protein electrophoresis and immunofixation electrophoresis. These electrophoretic procedures can show restricted immunoglobulin migration, characterize the heavy and/or light chains, and quantitate the monoclonal protein. Some monoclonal proteins, however, are difficult to identify and quantitate by electrophoretic assays. The serum concentration of monoclonal free light chains for example may not be high enough to be recognized or quantitated. Immunoassays that are specific for free light chains, as opposed to light chains bound to heavy chains, can quantitate kappa and lambda free light chains. An
abnormal ratio of the free light chains can identify excess clonal plasma cell proliferation and the concentration of the monoclonal free light chain can be determined. Another example of proteins that are difficult to identify and quantitate are monoclonal proteins that are intact immunoglobulins (heavy and light chains) that migrate very broadly in the gamma fraction or migrate within the beta or alpha fractions. Immunoassays that are specific for heavy and light chain pairs (HLC) such as IgM kappa or IgM lambda can quantitate the individual HLC pairs and be used to identify abnormal ratios of the HLC pairs and to quantitate the monoclonal HLC pair.

**Useful For:** The quantitation of heavy and light chain pairs is useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses 2. Quantitating monoclonal IgM proteins that are difficult to quantitate on serum protein electrophoresis 3. Providing a more specific quantitation of the monoclonal protein than quantitating total IgM

**Interpretation:** An elevated IgM heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgM kappa clone of plasma cells. A low IgM HLC pair ratio suggests a clonal proliferation of an IgM lambda clone of plasma cells.

**Reference Values:**

Total IgM

<table>
<thead>
<tr>
<th>Age</th>
<th>Range (mg/dL)</th>
</tr>
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<tbody>
<tr>
<td>0-&lt;5 months</td>
<td>26-122</td>
</tr>
<tr>
<td>5-&lt;9 months</td>
<td>32-132</td>
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<td>9-&lt;15 months</td>
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<td>15-&lt;24 months</td>
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<td>2-&lt;4 years</td>
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<td>4-&lt;7 years</td>
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<td>45-244</td>
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<tr>
<td>16-&lt;18 years</td>
<td>49-201</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>37-286</td>
</tr>
</tbody>
</table>

IgM kappa: 22-161 mg/dL

IgM lambda: 10-94 mg/dL

MK/ML ratio: 0.7900-4.61


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**Immunoglobulin M (IgM), Serum**

**Clinical Information:** The gamma-globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 5% is immunoglobulin M (IgM). Elevations of IgM may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgM occur in macroglobulinemia. Monoclonal gammopathies of all types may lead to a spike in the gamma-globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detecting or monitoring of monoclonal gammopathies and immune deficiencies

**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin M may occur in monoclonal gammopathies such as macroglobulinemia, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary
immune deficiencies.

**Reference Values:**

- 0-<5 months: 26-122 mg/dL
- 5-<9 months: 32-132 mg/dL
- 9-<15 months: 40-143 mg/dL
- 15-<24 months: 46-152 mg/dL
- 2-<4 years: 37-184 mg/dL
- 4-<7 years: 37-224 mg/dL
- 7-<10 years: 38-251 mg/dL
- 10-<13 years: 41-255 mg/dL
- 13-<16 years: 45-244 mg/dL
- 16-<18 years: 49-201 mg/dL
- > or =18 years: 37-286 mg/dL

**Clinical References:**


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**Immunoglobulin Subclass IgG4, Serum**

**Clinical Information:** The most abundant immunoglobulin isotype in human serum is immunoglobulin G (IgG). IgG immunoglobulins are comprised of 4 subclasses designated IgG1 through IgG4. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Each IgG subclass contains structurally unique portions of the constant region of the gamma heavy chain. IgG subclass 4-related disease is a recently recognized syndrome of unknown etiology most often occurring in middle-aged and older men. Several organ systems can be involved and encompasses many previous and newly described diseases such as type I autoimmune pancreatitis; Mikulicz disease and sclerosing sialadenitis; inflammatory orbital psuedotumor; chronic sclerosing aortitis; Riedel thyroiditis, a subset of Hashimoto thyroiditis; IgG4-related interstitial pneumonitis; and IgG4-related tubulointerstitial nephritis. Each of these entities is characterized by tumorlike swelling of the involved organs with infiltrative, predominately IgG4-positive, plasma cells with accompanying "storiform" fibrosis. In addition, elevated serum concentrations of IgG4 are found in 60% to 70% of patients diagnosed with IgG4-related disease. The diagnosis of IgG4-related disease requires a tissue biopsy of the affected organ demonstrating the aforementioned histological features. It is recommended that patients suspected of having an IgG4-related disease have their serum IgG4 level measured.

**Useful For:** Supporting the diagnosis of IgG4-related disease

**Interpretation:** Elevated levels of IgG4 are consistent with, but not diagnostic of, IgG4-related disease.

**Reference Values:**

- 0-<5 months: < or =19.8 mg/dL
- 5-<9 months: < or =20.8 mg/dL
- 9-<15 months: < or =22.0 mg/dL
- 15-<24 months: < or =23.0 mg/dL
- 2-<4 years: 0.4-49.1 mg/dL
- 4-<7 years: 0.8-81.9 mg/dL
- 7-<10 years: 1.0-108.7 mg/dL
Immunoglobulin Total Light Chains, Urine

**Clinical Information:** Immunoglobulin light chains are usually cleared from blood through the renal glomeruli and reabsorbed in the proximal tubules so that urine light-chain concentrations are very low or undetectable. The production of large amounts of monoclonal light chains, however, can overwhelm this reabsorption mechanism. The detection of monoclonal light chains in the urine (Bence Jones proteinuria) has been used as a diagnostic marker for multiple myeloma since the report by Dr. H. Bence Jones in 1847. Current laboratory procedures employ protein electrophoresis and immunofixation for the identification and characterization of urine monoclonal light chains, and the monoclonal light chains may be present in large enough amounts to also be quantitated as an M-spike on protein electrophoresis. The electrophoretic M-spike is the recommended method of monitoring monoclonal gammopathies such as multiple myeloma. Monitoring the urine M-spike is especially useful in patients with light-chain multiple myeloma in whom the serum M-spike is very small or absent, but the urine M-spike is large. Just as quantitative serum immunoglobulins by immunonephelometry are a complement to M-spike quantitation by electrophoresis, this quantitative urine light-chain assay may be used to complement urine M-spike quantitation by electrophoresis.

**Useful For:** Monitoring patients whose urines demonstrate large M-spikes Confirming the quantitation of specimens that show M-spikes by electrophoresis Detecting urine monoclonal proteins and identification of specimens that need urine protein electrophoresis

**Interpretation:** A kappa/lambda (K/L) ratio >6.2 suggests the presence of monoclonal kappa light chains. A K/L ratio <0.7 suggests the presence of monoclonal lambda light chains. In 24-hour specimens, a >90% increase in concentration suggests progression or relapse; a >90% decrease suggests treatment response. Increased kappa and/or lambda light chains may be seen in benign (polyclonal) and neoplastic (monoclonal) disorders.

**Reference Values:**
KAPPA TOTAL LIGHT CHAIN
<0.9 mg/dL

LAMBDA TOTAL LIGHT CHAIN
<0.7 mg/dL

KAPPA/LAMBDA RATIO
0.7-6.2

**Clinical References:**
electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is immunoglobulin G (IgG), 15% is immunoglobulin A (IgA), 5% is immunoglobulin M (IgM), 0.2% is immunoglobulin D (IgD), and a trace is immunoglobulin E (IgE). Elevations of IgG, IgA, and IgM may be due to polyclonal immunoglobulin production. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgG, IgA, IgD, and IgE characterize multiple myeloma. Monoclonal elevations of IgM occur in macroglobulinemia. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detecting or monitoring of monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevations of immunoglobulin G (IgG), immunoglobulin A (IgA), or immunoglobulin M (IgM) may occur in monoclonal gammopathies such as multiple myeloma (IgG, IgA), macroglobulinemia (IgM), primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:

IgG
0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL
16-<18 years: 503-1,719 mg/dL
> or =18 years: 767-1,590 mg/dL

IgA
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

IgM
0-<5 months: 26-122 mg/dL
5-<9 months: 32-132 mg/dL
9-<15 months: 40-143 mg/dL
15-<24 months: 46-152 mg/dL
2-<4 years: 37-184 mg/dL
4-<7 years: 37-224 mg/dL
7-<10 years: 38-251 mg/dL
10-<13 years: 41-255 mg/dL
13-<16 years: 45-244 mg/dL
16-<18 years: 49-201 mg/dL
> or =18 years: 37-286 mg/dL

FIMMC

Immunoglobulins, CSF Quantitative

Reference Values:
Immunoglobulin M CSF   (0.0 - 0.7) mg/dL
Immunoglobulin G CSF   (0.0 - 6.0) mg/dL
Immunoglobulin A CSF   (0.0 - 0.7) mg/dL

FUIQL

Indicans, Urine Qualitative

Clinical Information: Indole is produced by bacterial action on tryptophan in the small intestine. Most is eliminated in the feces; the remainder is absorbed and detoxified in the liver and excreted as indican (indoxyl sulfate) in the urine. The amount of indican normally excreted in the urine is small. However, large amounts are produced as a results of high protein diets and in various disorders such as Hartnup disease, intestinal obstruction, gastric cancer, hypochlorhydria, biliary obstruction, and malabsorptive conditions such as sprue and blind-loop syndrome.

Reference Values:
Negative

MONOS

Infectious Mononucleosis, Rapid Test, Serum

Clinical Information: Infectious mononucleosis (IM) is a viral illness that involves reticuloendothelial tissue and is generally limited to children and young adults. IM is most commonly caused by Epstein-Barr virus (EBV). The disease is characterized by fever, sore throat, lymphadenopathy, headache, and fatigue, and on a symptomatic basis may be confused with other diseases. Detectable levels of unique heterophile antibodies are produced in patients with IM.

Useful For: Rapid confirmation of a diagnosis of infectious mononucleosis

Interpretation: Detectable levels of the infectious mononucleosis (IM) heterophile antibody can usually be expected to occur between the sixth and tenth day following the onset of symptoms. The level usually increases through the second or third week of illness and, thereafter, can be expected to persist, gradually declining over a 12-month period.

Reference Values:
Negative (reported as positive or negative)


IBDP

Inflammatory Bowel Disease Serology Panel, Serum
Clinical Information: The term "inflammatory bowel disease" (IBD) is often used to refer to 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD), that produce inflammation of the large or small intestines. The diagnosis of these 2 diseases is based on clinical features, the results of barium X-rays, colonoscopy, mucosal biopsy histology, and in some cases operative findings and resected bowel pathology and histology. Recently, patients with IBD have been shown to have antibodies in serum that help to distinguish between CD and UC.(1) Patients with UC often have measurable neutrophil specific antibodies (NSA), which react with as yet uncharacterized target antigens in human neutrophils; whereas, patients with CD often have measurable antibodies of the IgA and/or IgG isotypes, which react with cell wall mannan of Saccharomyces cerevisiae strain Su 1.

Useful For: As an adjunct in the diagnosis of ulcerative colitis and Crohn's disease in patients suspected of having inflammatory bowel disease

Interpretation: The finding of neutrophil specific antibodies (NSA) with normal levels of IgA and IgG anti-Saccharomyces cerevisiae antibodies (ASCA) is consistent with the diagnosis of ulcerative colitis (UC); the finding of negative NSA with elevated IgA and IgG ASCA is consistent with Crohn's disease (CD). NSA are detectable in approximately 50% of patients with UC, and elevated levels of either IgA or IgG ASCA occur in approximately 55% of patients with CD. Approximately 40% of patients with CD have elevated levels of both IgA and IgG ASCA. Employed together, the tests for NSA and ASCA have the following positive predictive values (PV) for UC and CD, respectively: NSA positive with normal levels of IgA and IgG ASCA, PV of 91%; NSA negative with elevated levels if IgA and IgG ASCA, PV of 90%.(2)

Reference Values:
Saccharomyces cerevisiae ANTIBODY, IgA
Negative: < or =20.0 U
Equivocal: 20.1-24.9 U
Weakly positive: 25.0-34.9 U
Positive: > or =35.0 U

Saccharomyces cerevisiae ANTIBODY, IgG
Negative: < or =20.0 U
Equivocal: 20.1-24.9 U
Weakly positive: 25.0-34.9 U
Positive: > or =35.0 U

NEUTROPHIL-SPECIFIC ANTIBODIES
Negative (not detectable)


Inflammatory Myofibroblastic Tumors (IMT), 2p23 (ALK) Rearrangement, FISH, Tissue

Clinical Information: Inflammatory myofibroblastic tumor (IMT) is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils which occur primarily in the soft tissue and viscera of children and young adults. They may arise in any anatomical site including lung, soft tissue, retroperitoneum, and bladder. The genetic mechanisms underlying IMT pathogenesis are only partially known, but cytogenetic analyses have disclosed chromosomal rearrangements involving the ALK gene at 2p23. Studies support that identification of ALK gene rearrangement is useful to differentiate IMTs from other spindle cell neoplasms of soft tissue and viscera.
**Useful For:** Supporting the diagnosis of inflammatory myofibroblastic tumor when used in conjunction with an anatomic pathology consultation.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result is consistent with a subset of inflammatory myofibroblastic tumor (IMT). A negative result suggests that an ALK gene rearrangement is not present but does not exclude the diagnosis of IMT.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Infliximab Quantitation with Reflex to Antibodies to Infliximab, Serum**

**Clinical Information:** Infliximab (Remicade, Janssen Biotech) is a chimeric immunoglobulin (IgG1 kappa) targeting tumor necrosis factor-alpha (TNF-a), and is currently FDA-approved for the treatment of multiple inflammatory conditions. Infliximab binds to soluble TNF-a and transmembrane homotrimers. Infliximab pharmacokinetic properties may vary with disease and clearance is affected by concomitant use of immunosuppressants, high concentrations of TNF-a and C-reactive proteins,(1,2) low albumin concentrations, high body mass index, and presence of antibodies-to-infliximab, also known as human antichimeric antibodies (HACA).(3) Males seem to clear infliximab faster than females.(3) Several studies have demonstrated that infliximab quantitation in the setting of loss of response to therapy can aid in patient management, as trough concentrations defined as therapeutic have been associated with superior clinical response and improved prognosis.(4-6)

**Useful For:** Trough level quantitation for evaluation of patients with loss of response to infliximab.

**Interpretation:** Low trough concentrations may be correlated with loss of response to infliximab. For infliximab trough concentrations < or =5.0 mcg/mL, testing for antibodies to infliximab (ATI) is suggested. For infliximab trough concentrations >5.0 mcg/mL, presence of ATI is unlikely; patients experiencing loss of response to infliximab may benefit from an increased dose or a shorter infusion interval. Results >35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough.

**Reference Values:**
Limit of quantitation is 1.0 mcg/mL. Therapeutic ranges are disease specific.

**Clinical References:**
5. Imaeda H, Bamba S, Takahashi K, et al: Relationship between serum infliximab trough levels and...

**FH1N1**

**Influenza A H1N1 (2009) Real-Time RT-PCR**

**Reference Values:**
Reference Range: Not Detected

**SFLA**

**Influenza Virus A Antibodies, IgG and IgM (Separate Determinations), Serum**

**Clinical Information:** Influenza is usually a mild illness of the upper respiratory tract. Involvement of the lower respiratory tract, however, can lead to 4 types of clinical syndromes: physical signs of lower respiratory tract involvement without roentgenographic evidence of pneumonia, influenza complicated by bacterial pneumonia, primary influenza virus pneumonia, and combined inflenzenzal and bacterial pneumonias. Influenza virus infections are most severe in patients with certain preexisting conditions such as rheumatic heart disease, bronchopulmonary disease, impaired renal function, and diabetes mellitus. Infections can be more severe in elderly patients, pregnant females, and immunocompromised patients. Influenza virus type A can produce serious illness during the first 2 years of life, with croup, bronchitis, and pneumonia being prominent. Influenza A may also precipitate asthmatic attacks and produce chronic pulmonary complications in children.

**Interpretation:** The presence of IgM class antibody or a 4-fold or greater rise in titer in paired (acute and convalescent) sera indicates recent infection. The presence of IgG class antibody generally indicates past exposure.

**Reference Values:**
IgG: <1:10
IgM: <1:10


**SFLB**

**Influenza Virus B Antibodies, IgG and IgM (Separate Determinations), Serum**

**Clinical Information:** Influenza is usually a mild illness of the upper respiratory tract. Involvement of the lower respiratory tract, however, can lead to 4 types of clinical syndromes; physical signs of lower respiratory tract involvement without roentgenographic evidence of pneumonia, influenza complicated by bacterial pneumonia, primary influenza virus pneumonia, and combined influenza and bacterial pneumonias. Influenza virus infections are most severe in patients with certain preexisting conditions such as rheumatic heart disease, bronchopulmonary disease, impaired renal function, and diabetes mellitus. Infections can be more severe in elderly patients, pregnant females, and immunocompromised patients. Influenza virus type B generally produces less severe disease than type A. Outbreaks of influenza type B virus are usually more localized than type A. Both infections occur in the United States between November and March. Influenza A is susceptible to antiviral activity of amantadine while influenza B is not inhibited by this drug.

**Useful For:** Diagnosis of recent infection by influenza virus type B when isolation of the organism by culture is unsuccessful
**Interpretation:** The presence of IgM class antibody or a 4-fold or greater rise in titer in paired (acute and convalescent) sera indicates recent infection. The presence of IgG class antibody alone generally indicates past exposure.

**Reference Values:**
IgG: <1:10
IgM: <1:10


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**Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR**

**Clinical Information:** Influenza, otherwise known as the “flu,” is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness/fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously “swine” flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. The CDC now predicts that the influenza season will return to a winter distribution. Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA), and the adamantanes, rimantadine and amantadine. These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults. RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA. Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

**Useful For:** Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test

**Interpretation:** A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis.

**Reference Values:**
Not applicable

**Clinical References:** 1. Centers for Disease Control and Prevention. Seasonal Influenza:
Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Miscellaneous Sources

Clinical Information: Influenza, otherwise known as the “flu,” is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness/fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year.(1) In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously “swine” flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years.(1) Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults.(4) RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA.(2,3) Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

Useful For: Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test

Interpretation: A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

Reference Values:
Negative

Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Nasopharyngeal Swab

**Clinical Information:** Influenza, otherwise known as the “flu,” is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness/fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years. Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults. RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA. Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

**Useful For:** Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test

**Interpretation:** A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

**Reference Values:**
Negative

Influenza Virus Type A and Type B, Molecular Detection, PCR

Clinical Information: Influenza, otherwise known as the "flu," is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness/fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. The CDC now predicts that the influenza season will return to a winter distribution. Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA), and the adamantanes, rimantadine and amantadine. These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A and influenza B. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA. Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

Useful For: Rapid and accurate detection of influenza A and influenza B in a single test

Interpretation: A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis.

Reference Values: Not applicable

tests are normal. Rotor syndrome is a rare condition of the liver and very similar to DJS. It is inherited as an autosomal recessive trait caused by digenic inheritance of homozygous mutations in the SLCO1B1 and SLCO1B3 genes. Biochemically, Rotor syndrome can be distinguished from DJS by a normal functioning gallbladder, normal liver histology, and the different pattern of coproporphyrin isomers excretion. In healthy individuals, the percent of coproporphyrin I excreted relative to the total coproporphyrin excreted in urine is approximately 20% to 45%. In DJS and Rotor syndrome, retention of coproporphyrin III by the liver causes diminished urinary excretion. Consequently the percent of coproporphyrin I to the total coproporphyrin excreted in the urine exceeds the normal range. When the total urinary excretion of coproporphyrin is elevated and the percent of coproporphyrin I to total coproporphyrin exceeds 60%, but is less than 80%, the presentation is most consistent with Rotor syndrome. In patients with DJS, the percentage of coproporphyrin I to total coproporphyrin is typically greater than 80% and the total urinary coproporphyrin excretion is within normal limits. Some overlap may exist so the ratio alone should not be used to distinguish between Rotor or DJS.

**Useful For:** Differential diagnosis of hyperbilirubinemia syndromes between Dubin-Johnson syndrome and Rotor syndrome in patients ≥1 year of age

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

**COPROPORPHYRIN ISOMERS I AND III**

<table>
<thead>
<tr>
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<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>25-150 mcg/24 hours</td>
</tr>
<tr>
<td>Females</td>
<td>8-110 mcg/24 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% COPROPORPHYRIN I</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-45%</td>
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</tbody>
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**Clinical References:**


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**INHAB 86336**

**Inhibin A and B, Tumor Marker, Serum**

**Clinical Information:** See Individual Unit Codes

**Useful For:** See Individual Unit Codes

**Interpretation:** See Individual Unit Codes

**Reference Values:**

**INHIBIN A, TUMOR MARKER**

<table>
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<td>&lt;2.0 pg/mL</td>
</tr>
<tr>
<td>Females</td>
<td>&lt;4.7 pg/mL</td>
</tr>
<tr>
<td>&lt;11 years</td>
<td>&lt;97.5 pg/mL</td>
</tr>
<tr>
<td>11-17 years</td>
<td>&lt;97.5 pg/mL</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>&lt;97.5 pg/mL</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>&lt;2.1 pg/mL</td>
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**INHIBIN B**

<table>
<thead>
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<th>Gender</th>
<th>Value</th>
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<tr>
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<td></td>
</tr>
</tbody>
</table>
0-23 months: <430 pg/mL
2-4 years: <269 pg/mL
5-7 years: <184 pg/mL
8-10 years: <214 pg/mL
11-13 years: <276 pg/mL
14-17 years: <273 pg/mL
Adults: <399 pg/mL

Females
0-23 months: <111 pg/mL
2-4 years: <44 pg/mL
5-7 years: <27 pg/mL
8-10 years: <67 pg/mL
11-13 years: <120 pg/mL
14-17 years: <136 pg/mL
Premenopausal
Follicular: <139 pg/mL
Luteal: <92 pg/mL
Postmenopausal: <10 pg/mL

Clinical References: See Individual Unit Codes

INHA 81049

Inhibin A, Tumor Marker, Serum

Clinical Information: Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in the female and Sertoli cells of the testis in the male. They selectively suppress the secretion of pituitary follicle stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum; whereas inhibin B is predominantly produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial, stromal sex cord, and germ cell tumors. Epithelial ovarian tumors account for 90% of cases and are further subdivided into: serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex cord tumors, which account for 2% to 5% of all ovarian tumors. Elevations of serum inhibin A and/or B are detected in some patients with granulosa cell tumors. Inhibin A elevations have been reported in approximately 70% of granulosa cell tumors. In these patients, inhibin A levels tend to show a 6-fold to 7-fold increase over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin A also appears to be suitable markers for epithelial tumors of the mucinous type with about 20% of cases having elevated inhibin A levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be a complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels for both proteins are normally very low. Inhibin A has limited utility as an ovarian cancer marker in premenopausal women, where circulating levels are higher and fluctuate throughout the menstrual cycle and, therefore, are difficult to interpret.

Useful For: An aid in the diagnosis of patients with granulosa cell tumors of the ovary when used in combination with inhibin B Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to secrete inhibin A

Interpretation: Inhibin A levels are elevated in approximately 70% of patients with granulosa cell tumors and in approximately 20% of patients with epithelial ovarian tumors. A normal inhibin A level does not rule-out a mucinous or granulosa ovarian cell tumor. Testing for inhibin B in these cases might be informative as a higher proportion of mucinous or granulosa ovarian cell tumors will have an elevated
inhibin B level. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin A levels decrease shortly after surgery. Elevations of inhibin A after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin A elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin A.

**Reference Values:**

Males: <2.0 pg/mL  
Females  
<11 years: <4.7 pg/mL  
11-17 years: <97.5 pg/mL  
Premenopausal: <97.5 pg/mL  
Postmenopausal: <2.1 pg/mL  

**Clinical References:**  

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**Inhibin B, Serum**  

**Clinical Information:** Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in females and Sertoli cells of the testis in males. Inhibins selectively suppress the secretion of pituitary follicle-stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum, whereas inhibin B is primarily produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. Inhibin A is low in the early follicular phase and rises at ovulation to maximum levels in the midluteal phase. In contrast, inhibin B levels increase early in the follicular phase to reach a peak coincident with the onset of the midfollicular phase decline in FSH levels. Inhibin B levels decrease in the late follicular phase. There is a short-lived peak of the hormone 2 days after the midcycle luteinizing hormone (LH) peak. Inhibin B levels remain low during the luteal phase of the cycle. The timing of the inhibin B rise suggests that it plays a role in regulation of folliculogenesis via a negative feedback on the production of FSH. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial (80%), germ cell tumors (10%-15%), and stromal sex-cord tumors (5%-10%). Epithelial ovarian tumors are further subdivided into serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex-cord tumors. Elevations of serum inhibin A and/or B are detected in some patients with granulosa cell tumors. Inhibin B elevations have been reported in 89% to 100% of patients with granulosa cell tumors. In those patients, inhibin B levels tend to be elevated about 60-fold over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin B also appears to be a suitable serum marker for epithelial tumors of the mucinous type with about 55% to 60% having elevated inhibin B levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels of inhibin are normally very low. Inhibin levels vary in relation to the menstrual cycle and, therefore, are difficult to interpret in premenopausal women. Inhibin B has also been used as a marker of ovarian reserve. Every female is born with a specific number of follicles containing oocytes, a number that steadily and naturally declines with age. The number of follicles remaining in the ovary at any time is called the ovarian reserve. As ovarian reserve diminishes, it is increasingly more difficult for the hormones used for in vitro fertilization (IVF) to stimulate follicle development and, thus, the likelihood of successful oocyte retrieval, fertilization, and
embryo transfer decreases, all leading to a lower chance of conceiving. As part of an infertility evaluation, attempts are made to estimate a woman's ovarian reserve. Tests to assess ovarian reserve include: day 3 FSH, day 3 inhibin B, and antimullerian hormone levels. The amount of inhibin B measured in serum during the early follicular phase of the menstrual cycle (day 3) directly reflects the number of follicles in the ovary. Therefore, the higher the inhibin B, the more ovarian follicles present. The level of inhibin B that predicts a poor response to IVF treatment has not been established with this assay. In males, inhibin B levels are higher in men with apparently normal fertility than in those with infertility and abnormal spermatogenesis. Serum inhibin B, when used in combination with FSH, is a more sensitive marker of spermatogenesis than FSH alone. However, the optimal level of inhibin B to assess male infertility has not been established.

**Useful For:** As an aid in the diagnosis of granulosa cell tumors and mucinous epithelial ovarian tumors

**Interpretation:** Inhibin B levels are elevated in approximately 89% to 100% of patients with granulosa cell tumors and in approximately 55% to 60% of patients with epithelial ovarian tumors. A normal inhibin B level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin A in these cases might be informative. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin B levels decrease to very low or undetectable levels shortly after surgery. Elevations of inhibin B after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin B elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin B. For infertility evaluation, an inhibin B level in the postmenopausal range is suggestive of a diminished or depleted ovarian reserve.

**Reference Values:**

**Males**
- 0-23 months: <430 pg/mL
- 2-4 years: <269 pg/mL
- 5-7 years: <184 pg/mL
- 8-10 years: <214 pg/mL
- 11-13 years: <276 pg/mL
- 14-17 years: <273 pg/mL
- Adults: <399 pg/mL

**Females**
- 0-23 months: <111 pg/mL
- 2-4 years: <44 pg/mL
- 5-7 years: <27 pg/mL
- 8-10 years: <67 pg/mL
- 11-13 years: <120 pg/mL
- 14-17 years: <136 pg/mL
- Premenopausal
  - Follicular: <139 pg/mL
  - Luteal: <92 pg/mL
- Postmenopausal: <10 pg/mL


**Insulin (Human), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

autoantibodies could displace bound insulin from the insulin autoantibodies, resulting in hypoglycemia. In addition to IgG and IgM insulin autoantibodies, IgE antibodies (identified by the fluorescence enzyme immunoassay) may occur. IgE insulin autoantibodies result in immediate hypersensitivity reactions, such as urticaria, but do not lead to insulin resistance or hypoglycemia as can be seen with the IgG antibodies. This test only determines the presence of IgG and IgM antibodies, not IgE antibodies. In conjunction with family history, HLA-typing and measurement of other islet cell autoantibodies (glutamic acid decarboxylase [GAD65] antibody and islet cell antigen 2 antibody [IA-2]), insulin autoantibody testing helps predict the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults. Inclusion of a recently described fourth autoantibody (zinc transporter 8, ZnT8) further enhances the prediction of type 1 diabetes occurrence and its distinction from type 2 diabetes.

**Useful For:** Predicting the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults, when used in conjunction with family history, HLA-typing, and other autoantibodies, including GD65S/81596 Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum and islet cell antigen 2 (IA-2) antibodies. Differential diagnosis of type 1 versus type 2 diabetes. Evaluating diabetes with insulin resistance in patients with established diabetes (type 1 or type 2). Investigation of hypoglycemia in nondiabetic subjects.

**Interpretation:** Seropositivity (> or =0.03 nmol/L) in a patient never treated with insulin is consistent with predisposition to type 1 diabetes. Seropositivity is not as informative of type 2 diabetes status as other islet cell antibodies in patients who are receiving (or have received) insulin therapy because this antibody can arise secondary to therapy. It is thought that high levels of insulin autoantibodies might contribute to insulin resistance. A family history of type 1 diabetes, other organ-specific autoimmunity and a diabetes-permissive HLA phenotype strengthens the prediction of type 1 diabetes development. The detection of multiple islet cell antibodies is indicative of the likely development of future type 1 diabetes. In patients presenting with hypoglycemia, the presence of insulin autoantibodies may indicate surreptitious insulin administration or, rarely, insulin autoantibody-related hypoglycemia. The differential diagnosis cannot be made on the basis of insulin autoantibody detection alone. C-peptide and insulin measurements are always required in addition to insulin autoantibody measurements in the diagnosis of hypoglycemia.

**Reference Values:**
< or =0.02 nmol/L
Reference values apply to all ages.

**Clinical References:**

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**Insulin, Free and Total, Serum**

**Clinical Information:** Insulin is produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Circulating insulin antibodies develop after diabetic patients are treated with exogenous insulin preparations. The presence of insulin antibodies has 2 main consequences: 1. Insulin antibodies will directly bind to insulin, making it unavailable for metabolic activity. 2. Insulin antibodies may adversely affect the binding characteristics of insulin in immunoassays, making reliable quantitation difficult. Free (bioactive) insulin could be measured after polyethylene glycol (PEG) precipitation of insulin antibodies and their bound insulin. If insulin antibodies are not present, the free and total insulin should be equivalent. The laboratory will report results of the total insulin (without PEG precipitation) and the free insulin (with PEG precipitation).

**Useful For:** Assessing free (bioactive) insulin concentrations in patients with known or suspected insulin antibodies.

**Interpretation:** If insulin antibodies are not present, the free and total insulin should be equivalent. A significant difference between total and free insulin is suggestive of the presence of insulin antibodies.
During prolonged fasting, when the patient's glucose is reduced to <40.0 mg/dL, elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. In patients with insulin-dependent diabetes mellitus, insulin levels generally decline. In the early stage of noninsulin dependent diabetes mellitus (NIDDM), insulin levels are either normal or elevated. In the late stage of NIDDM, insulin levels may also decline as levels of proinsulin decrease.

**Reference Values:**

Insulin, Free, S  
2.6-24.9 mcIU/mL

Insulin, Total, S  
2.6-24.9 mcIU/mL


**Insulin, Serum**

**Clinical Information:** Insulin is a hormone produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Type 1 diabetes (insulin-dependent diabetes) is caused by insulin deficiency due to destruction of insulin-producing pancreatic islet (beta) cells. Type 2 diabetes (noninsulin dependent diabetes) is characterized by resistance to the action of insulin (insulin resistance). Insulin levels may be increased in patients with pancreatic beta cell tumors (insulinoma).

**Useful For:** Diagnosing insulinoma, when used in conjunction with proinsulin and C-peptide measurements Management of diabetes mellitus

**Interpretation:** During prolonged fasting, when the patient's glucose level is reduced to <40 mg/dL, elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. Insulin levels generally decline in patients with type 1 diabetes mellitus. In the early stage of type 2 diabetes, insulin levels are either normal or elevated. In the late stage of type 2 diabetes, insulin levels decline. In normal individuals, insulin levels parallel blood glucose levels. To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio): -Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L. -Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L.

**Reference Values:**

2.6-24.9 mcIU/mL


**Insulin-Like Growth Factor 1 (IGF1), LC-MS and Insulin-Like Growth Factor-Binding Protein 3 (IGFBP3) Growth Panel**

**Clinical Information:** Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight 7.6 kDa). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, but the liver is the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular insulin-like growth factor-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. IGFBP3 is a 264-amino acid peptide (MW 29kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport, and control bioavailability and
half-life of IGFs, in particular IGF1, the major mediator of the anabolic- and growth-promoting effects of GH. In addition to its IGF binding-function, IGFBP3 also exhibits intrinsic growth-regulating effects that are not yet fully understood, but have evoked interest with regards to a possible role of IGFBP3 as a prognostic tumor marker. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious mutations in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate nutrition.

**Useful For:** Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment Insulin-like growth factor binding protein 3 can be used as a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism.

**Interpretation:** Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity, and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little if anything to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (Standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease.
activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

**Reference Values:**
**INSULIN-LIKE GROWTH FACTOR 1**

**Males:**
- 0-11 months: 18-156 ng/mL
- 1 year: 14-203 ng/mL
- 2 years: 16-222 ng/mL
- 3 years: 22-229 ng/mL
- 4 years: 30-236 ng/mL
- 5 years: 39-250 ng/mL
- 6 years: 47-275 ng/mL
- 7 years: 54-312 ng/mL
- 8 years: 61-356 ng/mL
- 9 years: 67-405 ng/mL
- 10 years: 73-456 ng/mL
- 11 years: 79-506 ng/mL
- 12 years: 84-551 ng/mL
- 13 years: 90-589 ng/mL
- 14 years: 95-618 ng/mL
- 15 years: 99-633 ng/mL
- 16 years: 104-633 ng/mL
- 17 years: 107-615 ng/mL
- 18-22 years: 91-442 ng/mL
- 23-25 years: 66-346 ng/mL
- 26-30 years: 60-329 ng/mL
- 31-35 years: 54-310 ng/mL
- 36-40 years: 48-292 ng/mL
- 41-45 years: 44-275 ng/mL
- 46-50 years: 40-259 ng/mL
- 51-55 years: 37-245 ng/mL
- 56-60 years: 34-232 ng/mL
- 61-65 years: 33-220 ng/mL
- 66-70 years: 32-209 ng/mL
- 71-75 years: 32-200 ng/mL
- 76-80 years: 33-192 ng/mL
- 81-85 years: 33-185 ng/mL
- 86-90 years: 33-179 ng/mL
- >91 years: 32-173 ng/mL

**Females:**
- 0-11 months: 14-192 ng/mL
- 1 year: 23-243 ng/mL
- 2 years: 28-256 ng/mL
- 3 years: 31-249 ng/mL
- 4 years: 33-237 ng/mL
- 5 years: 36-234 ng/mL
- 6 years: 39-246 ng/mL
- 7 years: 44-279 ng/mL
- 8 years: 51-334 ng/mL
- 9 years: 61-408 ng/mL
- 10 years: 73-495 ng/mL
- 11 years: 88-585 ng/mL
- 12 years: 104-665 ng/mL
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 years</td>
<td>120-719 ng/mL</td>
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<tr>
<td>14 years</td>
<td>136-729 ng/mL</td>
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<tr>
<td>15 years</td>
<td>147-691 ng/mL</td>
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<td>16 years</td>
<td>153-611 ng/mL</td>
</tr>
<tr>
<td>17 years</td>
<td>149-509 ng/mL</td>
</tr>
<tr>
<td>18-22 years</td>
<td>85-370 ng/mL</td>
</tr>
<tr>
<td>23-25 years</td>
<td>73-320 ng/mL</td>
</tr>
<tr>
<td>26-30 years</td>
<td>66-303 ng/mL</td>
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<td>31-35 years</td>
<td>59-279 ng/mL</td>
</tr>
<tr>
<td>36-40 years</td>
<td>54-258 ng/mL</td>
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<td>41-45 years</td>
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<tr>
<td>46-50 years</td>
<td>44-227 ng/mL</td>
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<tr>
<td>51-55 years</td>
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<td>61-65 years</td>
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<td>66-70 years</td>
<td>34-194 ng/mL</td>
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<td>71-75 years</td>
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<td>76-80 years</td>
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<td>86-90 years</td>
<td>33-175 ng/mL</td>
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<tr>
<td>&gt;or=91 years</td>
<td>25-179 ng/mL</td>
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**Tanner Stage Reference Ranges:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>81-255 ng/mL</td>
</tr>
<tr>
<td>II</td>
<td>106-432 ng/mL</td>
</tr>
<tr>
<td>III</td>
<td>245-511 ng/mL</td>
</tr>
<tr>
<td>IV</td>
<td>223-578 ng/mL</td>
</tr>
<tr>
<td>V</td>
<td>227-518 ng/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>86-323 ng/mL</td>
</tr>
<tr>
<td>II</td>
<td>118-451 ng/mL</td>
</tr>
<tr>
<td>III</td>
<td>258-529 ng/mL</td>
</tr>
<tr>
<td>IV</td>
<td>224-586 ng/mL</td>
</tr>
<tr>
<td>V</td>
<td>188-512 ng/mL</td>
</tr>
</tbody>
</table>


**Note:** Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

**INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 3**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7 days</td>
<td>&lt; or =0.7 mcg/mL</td>
</tr>
<tr>
<td>8-14 days</td>
<td>0.5-1.4 mcg/mL</td>
</tr>
<tr>
<td>15 days-11 months</td>
<td>unavailable</td>
</tr>
<tr>
<td>1 year</td>
<td>0.7-3.6 mcg/mL</td>
</tr>
<tr>
<td>2 years</td>
<td>0.8-3.9 mcg/mL</td>
</tr>
<tr>
<td>3 years</td>
<td>0.9-4.3 mcg/mL</td>
</tr>
<tr>
<td>4 years</td>
<td>1.0-4.7 mcg/mL</td>
</tr>
<tr>
<td>5 years</td>
<td>1.1-5.2 mcg/mL</td>
</tr>
<tr>
<td>6 years</td>
<td>1.3-5.6 mcg/mL</td>
</tr>
<tr>
<td>7 years</td>
<td>1.4-6.1 mcg/mL</td>
</tr>
</tbody>
</table>
8 years: 1.6-6.5 mcg/mL
9 years: 1.8-7.1 mcg/mL
10 years: 2.1-7.7 mcg/mL
11 years: 2.4-8.4 mcg/mL
12 years: 2.7-8.9 mcg/mL
13 years: 3.1-9.5 mcg/mL
14 years: 3.3-10 mcg/mL
15 years: 3.5-10 mcg/mL
16 years: 3.4-9.5 mcg/mL
17 years: 3.2-8.7 mcg/mL
18 years: 3.1-7.9 mcg/mL
19 years: 2.9-7.3 mcg/mL
20 years: 2.9-7.2 mcg/mL
21-25 years: 3.4-7.8 mcg/mL
26-30 years: 3.5-7.6 mcg/mL
31-35 years: 3.5-7.0 mcg/mL
36-40 years: 3.4-6.7 mcg/mL
41-45 years: 3.3-6.6 mcg/mL
46-50 years: 3.3-6.7 mcg/mL
51-55 years: 3.4-6.8 mcg/mL
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:
Males
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.8-6.9 mcg/mL
Stage III: 3.9-9.4 mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.7-9.1 mcg/mL

Females
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL
Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL

Note: Puberty onset, ie the transition from Tanner stage 1 (prepubertal) to Tanner stage 2 (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage 5 (young adult) should be reached by age 18.

Clinical References:

**FIGF2 80758**

**Insulin-like Growth Factor 2 (IGF-2)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range (ng/mL)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>258 â€“ 882</td>
<td>570</td>
</tr>
<tr>
<td>Pubertal</td>
<td>273 â€“ 892</td>
<td>583</td>
</tr>
<tr>
<td>Adults</td>
<td>333 â€“ 967</td>
<td>650</td>
</tr>
</tbody>
</table>

**IGFMS 62750**

**Insulin-Like Growth Factor-1, LC-MS, Serum**

**Clinical Information:** Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight kDa; Uniprot Accession P05019 [aa 49-118]). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, but the liver is the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular insulin-like growth factor-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild-to-moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious mutations in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate
nutrition.

**Useful For:** Evaluation of growth disorders Evaluation of growth hormone deficiency or excess in children and adults Monitoring of recombinant human growth hormone treatment Follow-up of individuals with acromegaly and gigantism

**Interpretation:** Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity, and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little if anything to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (Standard deviation score, Z-score of < -2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (e.g., exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-1 concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

**Reference Values:**

**Males:**
- 0-11 months: 18-156 ng/mL
- 1 year: 14-203 ng/mL
- 2 years: 16-222 ng/mL
- 3 years: 22-229 ng/mL
- 4 years: 30-236 ng/mL
- 5 years: 39-250 ng/mL
- 6 years: 47-275 ng/mL
- 7 years: 54-312 ng/mL
- 8 years: 61-356 ng/mL
- 9 years: 67-405 ng/mL
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- 11 years: 79-506 ng/mL
- 12 years: 84-551 ng/mL
- 13 years: 90-589 ng/mL
- 14 years: 95-618 ng/mL
- 15 years: 99-633 ng/mL
- 16 years: 104-633 ng/mL
- 17 years: 107-615 ng/mL
- 18-22 years: 91-442 ng/mL
- 23-25 years: 66-346 ng/mL
- 26-30 years: 60-329 ng/mL
- 31-35 years: 54-310 ng/mL
- 36-40 years: 48-292 ng/mL
- 41-45 years: 44-275 ng/mL

**Current as of July 8, 2016 11:28 am CDT**

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
46-50 years: 40-259 ng/mL
51-55 years: 37-245 ng/mL
56-60 years: 34-232 ng/mL
61-65 years: 33-220 ng/mL
66-70 years: 32-209 ng/mL
71-75 years: 32-200 ng/mL
76-80 years: 33-192 ng/mL
81-85 years: 33-185 ng/mL
86-90 years: 33-179 ng/mL
>91 years: 32-173 ng/mL

Females:
0-11 months: 14-192 ng/mL
1 year: 23-243 ng/mL
2 years: 28-256 ng/mL
3 years: 31-249 ng/mL
4 years: 33-237 ng/mL
5 years: 36-234 ng/mL
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51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:
Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL
Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL


Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References:

Insulin-Like Growth Factor-Binding Protein 3 (IGFBP-3), Serum

Clinical Information:
Insulin-like growth factor-binding protein-3 (IGFBP-3) is a 264-amino acid peptide (MW 29 kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport, and control bioavailability and half-life of insulin-like growth factors (IGF), in particular IGF-1, the major mediator of the anabolic- and growth-promoting effects of growth hormone (GH). Noncomplexed IGFBP-3 and IGF-1 have short half-lives (t1/2) of 30 to 90 minutes, and 10 minutes, respectively, while the IGFBP-3/IGF-1 complex is cleared with a much slower t1/2 of 12 hours. In addition to its IGF-binding function, IGFBP-3 also exhibits intrinsic growth-regulating effects that are not yet fully understood, but have evoked interest with regards to a possible role of IGFBP-3 as a prognostic tumor marker. The secretion patterns of IGFBP-3 and IGF-1 mimic each other; their respective syntheses are primarily controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGFBP-3 and IGF-1 levels show only minor fluctuations. IGFBP-3 and IGF-1 serum levels therefore represent a stable and integrated measurement of GH production and tissue effect. Low IGFBP-3 and IGF-1 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF-1 and IGFBP-3 levels within the reference range. Severe childhood GH resistance is rare and usually due to GH-receptor defects. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections. The prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGFBP-3 and IGF-1 levels indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk, and diminished longevity. It is plausible, but
unproven, that long-term rhGH-overtreatment may result in similar adverse outcomes.

**Useful For:** Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment As a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism

**Interpretation:** For all applications, insulin-like growth factor 1 (IGF-1) measurement has generally been shown to have superior diagnostic sensitivity and specificity compared with insulin-like growth factor-binding protein 3 (IGFBP-3). IGFBP-3 testing should, therefore, usually be combined with IGF-1 testing. The combination of IGF-1 and IGFBP-3 measurements appears superior to determining either analyte alone in the diagnosis of growth hormone (GH) deficiency and resistance, and in the monitoring of recombinant human GH therapy. By contrast, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP-3 measurement adds little if anything to IGF-1 testing. IGF-1 and IGFBP-3 levels below the 2.5th percentile for age are consistent with GH deficiency or severe resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels are also low and show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels are substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of an endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF-1 and IGFBP-3 levels within the reference range, ideally within the middle to upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF-1 and IGFBP-3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF-1 levels correlate better with clinical disease activity than IGFBP-3 levels.

**Reference Values:**
- 1-7 days: < or =0.7 mcg/mL
- 8-14 days: 0.5-1.4 mcg/mL
- 15 days-11 months: unavailable
- 1 year: 0.7-3.6 mcg/mL
- 2 years: 0.8-3.9 mcg/mL
- 3 years: 0.9-4.3 mcg/mL
- 4 years: 1.0-4.7 mcg/mL
- 5 years: 1.1-5.2 mcg/mL
- 6 years: 1.3-5.6 mcg/mL
- 7 years: 1.4-6.1 mcg/mL
- 8 years: 1.6-6.5 mcg/mL
- 9 years: 1.8-7.1 mcg/mL
- 10 years: 2.1-7.7 mcg/mL
- 11 years: 2.4-8.4 mcg/mL
- 12 years: 2.7-8.9 mcg/mL
- 13 years: 3.1-9.5 mcg/mL
- 14 years: 3.3-10 mcg/mL
- 15 years: 3.5-10 mcg/mL
- 16 years: 3.4-9.5 mcg/mL
- 17 years: 3.2-8.7 mcg/mL
- 18 years: 3.1-7.9 mcg/mL
- 19 years: 2.9-7.3 mcg/mL
- 20 years: 2.9-7.2 mcg/mL
- 21-25 years: 3.4-7.8 mcg/mL
- 26-30 years: 3.5-7.6 mcg/mL
- 31-35 years: 3.5-7.0 mcg/mL
- 36-40 years: 3.4-6.7 mcg/mL
- 41-45 years: 3.3-6.6 mcg/mL
- 46-50 years: 3.3-6.7 mcg/mL
- 51-55 years: 3.4-6.8 mcg/mL

Current as of July 8, 2016 11:28 am CDT
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:
Males
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.8-6.9 mcg/mL
Stage III: 3.9-9.4 mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.7-9.1 mcg/mL
Females
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL
Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage I (prepubertal) to Tanner stage II (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.


FIFNY
57586
Interferon-gamma (IFN-y) Serum
Reference Values:
<2.0 pg/mL

FIL5P
57575
Interleukin - 5 (IL-5) Plasma
Reference Values:
<3.0 pg/mL

FINTA
91708
Interleukin 1a
Reference Values:
**Interleukin 1b**

**Reference Values:**
Less than 1.0 pg/mL

**Interleukin 2**

**Interpretation:** Interpretive Information: Cytokines Results are to be used for research purposes or in attempts to understand the pathophysiology of immune, infectious, or inflammatory disorders.

**Reference Values:**
<=12 pg/mL

**Interleukin 2 Receptor (CD25), Soluble**

**Interpretation:** Interpretive Information: Cytokines Results are to be used for research purposes or in attempts to understand the pathophysiology of immune, infectious, or inflammatory disorders.

**Reference Values:**
<=1033 pg/mL

**Interleukin 28B (IL28B) Polymorphism (rs12979860), Blood**

**Clinical Information:** Individuals with hepatitis C virus (HCV) genotype 1 infections have variable responses to treatment with pegylated-interferon and ribavirin combination therapy. Some individuals will respond to treatment with sustained viral response, while other patients have poor response and fail to achieve sustained viral clearance. Response to pegylated-interferon and ribavirin combination therapy in HCV genotype 1-infected individuals has been found to be closely associated with a single-nucleotide polymorphism (SNP), designated rs12979860, located 3 kilobases upstream from the interleukin 28B gene locus (IL28B) present on human chromosome 19. HCV genotype 1-infected individuals with the CC genotype, as compared to either the CT or TT genotypes, of this SNP in IL28B have approximately 2- to 3-fold greater rates of sustained viral response to combined pegylated-interferon and ribavirin therapy. Similar increases in sustained viral response rates were observed across various racial groups, including European Americans (95% CI, 1.8- to 2.3-fold), African Americans (95% CI, 1.9- to 4.7-fold), and Hispanics (95% CI, 1.4- to 3.2-fold). The CC genotype has also been associated with a 3-fold increase in rate of spontaneous clearance of HCV. The SNP in IL28B is only one of many factors that can influence response rates to pegylated-interferon and ribavirin combination therapy in HCV genotype 1 infection, and the SNP genotype result should be interpreted in the context of other clinical factors present in a given patient. Frequency of the rs12979860 C allele varies across different racial and ethnic groups. The rs12979860 C variant is most frequently present in individuals from East Asia (allele frequency >0.9) and least common in individuals of African origin (allele frequency 0.2-0.5). In a recent US-based study, the favorable CC genotype was observed in 37% of Caucasians, 29% Hispanics, and 14% of African Americans tested. The mechanism by which the IL28B genotype mediates response to pegylated-interferon and ribavirin combination therapy among HCV genotype 1-infected individuals is not yet understood and is the subject of intense ongoing research. The impact of the IL28B-related polymorphism on response rates in patients infected with HCV genotypes other than genotype 1 is still being investigated.

**Useful For:** Predicting responsiveness of genotype 1 hepatitis C viral infections to combined pegylated-interferon and ribavirin-based therapies

**Interpretation:** An interpretative report will be provided.
Interleukin 28B (IL28B) Polymorphism (rs12979860), Saliva

Clinical Information: Individuals with hepatitis C virus (HCV) genotype 1 infections have variable responses to treatment with pegylated-interferon and ribavirin combination therapy. Some individuals will respond to treatment with sustained viral response, while other patients have poor response and fail to achieve sustained viral clearance. Response to pegylated-interferon and ribavirin combination therapy in HCV genotype 1-infected individuals has been found to be closely associated with a single-nucleotide polymorphism (SNP), designated rs12979860, located 3 kilobases upstream from the interleukin 28B gene locus (IL28B) present on human chromosome 19. HCV genotype 1-infected individuals with the CC genotype, as compared to either the CT or TT genotypes, of this SNP in IL28B have approximately 2- to 3-fold greater rates of sustained viral response to combined pegylated-interferon and ribavirin therapy. Similar increases in sustained viral response rates were observed across various racial groups, including European Americans (95% CI, 1.8- to 2.3-fold), African Americans (95% CI, 1.9- to 4.7-fold), and Hispanics (95% CI, 1.4- to 3.2-fold). The CC genotype has also been associated with a 3-fold increase in rate of spontaneous clearance of HCV.(1) The SNP in IL28B is only one of many factors that can influence response rates to pegylated-interferon and ribavirin combination therapy in HCV genotype 1 infection, and the SNP genotype result should be interpreted in the context of other clinical factors present in a given patient. Frequency of the rs12979860 C allele varies across different racial and ethnic groups. The rs12979860 C variant is most frequently present in individuals from East Asia (allele frequency >0.9) and least common in individuals of African origin (allele frequency 0.2-0.5). In a recent US-based study, the favorable CC genotype was observed in 37% of Caucasians, 29% Hispanics, and 14% of African Americans tested. The mechanism by which the IL28B genotype mediates response to pegylated-interferon and ribavirin combination therapy among HCV genotype 1-infected individuals is not yet understood and is the subject of intense ongoing research. The impact of the IL28B-related polymorphism on response rates in patients infected with HCV genotypes other than genotype 1 is still being investigated.

Useful For: Predicting responsiveness of genotype 1 hepatitis C viral infections to combined pegylated-interferon and ribavirin-based therapies Genotyping patients who prefer not to have venipuncture done

Interpretation: An interpretative report will be provided.

Reference Values: An interpretive report will be provided

Interleukin 6
Reference Values:
< 5 pg/mL

Interleukin-10 (IL-10) Serum
Reference Values:
<2.0 pg/mL

Interleukin-4 (IL-4) Serum
Reference Values:
<2.0 pg/mL

Interleukin-6 (IL-6) Serum
Reference Values:
< 17.4 pg/mL

Interleukin-6, Highly Sensitive
Reference Values:
0.31 – 5.00 pg/mL

Interleukin-8 (IL-8) Serum
Reference Values:
<57.8 pg/mL

Intrinsic Factor Blocking Antibody, Serum
Clinical Information: The cobalamins, also referred to as vitamin B12, are a group of closely related enzymatic cofactors involved in the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A and in the synthesis of methionine from homocysteine. Vitamin B12 deficiency can lead to megaloblastic anemia and neurological deficits. The latter may exist without anemia, or precede it. Adequate replacement therapy will generally improve or cure cobalamin deficiency. Unfortunately, many other conditions, which require different interventions, can mimic the symptoms and signs of vitamin B12 deficiency. Moreover, even when cobalamin deficiency has been established, clinical improvement may require different dosages or routes of vitamin B12 replacement, depending on the underlying cause. In particular, patients with pernicious anemia (PA), possibly the commonest type of cobalamin deficiency in developed countries, require either massive doses of oral vitamin B12 or parenteral replacement therapy. The reason is that in PA patients suffer from gastric mucosal atrophy, most likely caused by a destructive autoimmune process. This results in diminished or absent gastric acid, pepsin and intrinsic factor (IF) production. Gastric acid and pepsin are required for liberation of cobalamin from binding proteins, while IF binds the free vitamin B12, carries it to receptors on the ileal mucosa, and facilitates its absorption. Most PA patients have autoantibodies against gastric parietal cells or intrinsic factor, with the latter being very specific but only present in approximately 50% of cases. By contrast, parietal cell antibodies are found in approximately 90% of PA patients, but are also found in a significant proportion of patients with other autoimmune diseases, and in approximately 2.5% (4th decade of life) to approximately 10% (8th decade of life) of healthy individuals.
Useful For: Confirming the diagnosis of pernicious anemia

Interpretation: The aim of the work-up of patients with suspected vitamin B12 deficiency is to first confirm the presence of deficiency and then to establish its most likely etiology. Measurement of serum vitamin B12, either preceded or followed by serum methylmalonic acid measurement, is the first step in diagnosing pernicious anemia (PA). If these tests support deficiency, then intrinsic factor blocking antibody (IFBA) testing is indicated to confirm PA as the etiology. A positive IFBA test supports very strongly a diagnosis of PA. Since the diagnostic sensitivity of IFBA testing for PA is only around 50%, an indeterminate or negative IFBA test does not exclude the diagnosis of PA. In these patients, either PA or another etiology, such as malnutrition, may be present. Measurement of serum gastrin levels will help in these cases. In patients with PA, fasting serum gastrin is elevated to >200 pg/mL in an attempted compensatory response to the achlorhydria seen in this condition. For a detailed overview of the optimal testing strategies in PA diagnosis, see ACASM / Pernicious Anemia Cascade, Serum, and associated Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:
Negative


UIOD 9549
Iodine, 24 Hour, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

Useful For: Monitoring iodine excretion rate as an index of daily iodine replacement therapy
Correlating total body iodine load with (131)I-uptake studies in assessing thyroid function

Interpretation: Daily urinary output <90 mcg/specimen suggests dietary deficiency. Values >1,000 mcg/specimen may indicate dietary excess, but more frequently suggest recent drug or contrast media exposure.

Reference Values:
0-15 years: not established
> or =16 years: 93-1,125 mcg/specimen


IODU 8639
Iodine, Random, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

Useful For: Monitoring iodine excretion rate as an index of daily iodine replacement therapy
Correlating total body iodine load with (131)I-uptake studies in assessing thyroid function

Interpretation: Daily urinary output <20 mcg/L suggest dietary deficiency. Values >1,000 mcg/L may indicate dietary excess, but more frequently suggest recent drug or contrast media exposure.

Reference Values:
0-15 years: not established

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**IOD 81574**

**Iodine, Serum**

**Clinical Information:** Iodine is an essential element that is required for thyroid hormone production. The measurement of iodine serves as an index of adequate dietary iodine intake and iodine overload, particularly from iodine-containing drugs such as amiodarone.

**Useful For:** Determination of iodine overload Monitoring iodine levels in individuals taking iodine-containing drugs

**Interpretation:** Values between 80 ng/mL and 250 ng/mL have been reported to indicate hyperthyroidism. Values >250 ng/mL may indicate iodine overload.

**Reference Values:**
- 40-92 ng/mL


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**ICRU 60440**

**Iodine/Creatinine Ratio, Random, Urine**

**Clinical Information:** Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

**Useful For:** Monitoring iodine excretion rate as an index of daily iodine replacement therapy Correlating total body iodine load with (131)I uptake studies in assessing thyroid function

**Interpretation:** Daily urinary output <70 mcg/g creatinine suggest dietary deficiency. Values >1,000 mcg/g creatinine may indicate dietary excess, but more frequently suggest recent drug or contrast media exposure.

**Reference Values:**
- 16-40 years: 70-530 mcg/g Creatinine
- 41-70 years: 70-860 mcg/g Creatinine
- >70 years: 70-1,150 mcg/g Creatinine

Reference values have not been established for patients that are <16 years of age.


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**HEXP 61713**

**Iohexol, Plasma**

**Clinical Information:** The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons.
**Useful For:** Determining glomerular filtration rate

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

**Iohexol, Timed Collection, Urine**

**Clinical Information:** The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons.

**Useful For:** Determining glomerular filtration rate

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

**Ipecac Use Markers**

**Reference Values:**
Therapeutic and toxic ranges have not been established.

Emetine and cephaeline are alkaloids present in ipecac.

Serum emetine levels within 2 hours of a 30 mL dose of ipecac syrup range from 0 - 75.0 ng/mL.

**Iron and Total Iron-Binding Capacity, Serum**

**Clinical Information:** Ingested iron is absorbed primarily from the intestinal tract and is temporarily stored in the mucosal cells as Fe(III)-ferritin. Ferritin provides a soluble protein shell to encapsulate a complex of insoluble ferric hydroxide-ferric phosphate. On demand, iron is released into the blood by mechanisms that are not clearly understood, to be transported as Fe(III)-transferrin. Transferrin is the primary plasma iron transport protein, which binds iron strongly at physiological pH. Transferrin is generally only 25% to 30% saturated with iron. The additional amount of iron that can be bound is the unsaturated iron-binding capacity (UIBC). The total iron binding capacity (TIBC) can be indirectly determined using the sum of the serum iron and UIBC. Knowing the molecular weight of the transferrin and that each molecule of transferrin can bind 2 atoms of iron, TIBC and transferrin concentration is interconvertible. Percent saturation (100 x serum iron/TIBC) is usually normal or increased in persons
who are iron deficient, pregnant, or are taking oral contraceptive medications. Persons with chronic inflammatory processes, hemochromatosis, or malignancies generally display low transferrin.

**Useful For:** Screening for chronic iron overload diseases, particularly hereditary hemochromatosis. Serum iron, total iron-binding capacity, and percent saturation are widely used for the diagnosis of iron deficiency. However, serum ferritin is a much more sensitive and reliable test for demonstration of iron deficiency.

**Interpretation:** In hereditary hemochromatosis, serum iron is usually >150 mcg/dL and percent saturation is >60%. In advanced iron overload states, the percent saturation often is >90%. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

**Reference Values:**

**IRON**
- Males: 50-150 mcg/dL
- Females: 35-145 mcg/dL

**TOTAL BINDING CAPACITY**
250-400 mcg/dL.

**PERCENT SATURATION**
14-50%

**Clinical References:**

**FET**
8350

**Iron, Liver Tissue**

**Clinical Information:** Hemosiderosis is the condition of excessive iron accumulation in tissues. Liver is the first organ affected in iron-overload diseases. Transient increases in iron first appear in Kupffer cells. This finding is commonly related to sideroblastic anemia, excessive iron consumption, or chronic alcohol ingestion. Persistent hemosiderosis, as seen in hemochromatosis, causes iron accumulation in hepatocytes, and is usually concentrated in biliary cells. Hereditary hemochromatosis is an autosomal recessive disease with estimated prevalence in the population of 2 in 1,000 in Caucasians, with lower incidence in other races. The gene responsible for hereditary hemochromatosis (HFE) is located on chromosome 6; the majority of hereditary hemochromatosis patients have mutations in this HFE gene. Hereditary hemochromatosis is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues that typically begins to be expressed in the third to fifth decades of life, but may occur in children. The most common presentation is hepatic cirrhosis in combination with hypopituitarism, cardiomyopathy, diabetes, arthritis, or hyperpigmentation. Because of the severe sequelae of this disease if left untreated and recognizing that treatment is relatively simple, early diagnosis before symptoms or signs appear is important. Screening for hemochromatosis is best done by measuring serum iron and transferrin saturation (FEC / Iron and Total Iron-Binding Capacity, Serum). If the serum iron concentration is >175 mcg/dL and the transferrin saturation is >55%, analysis of serum ferritin concentration (FERR / Ferritin, Serum) is indicated. A ferritin concentration >400 ng/mL is suggestive of hemochromatosis, but also can indicate other forms of hepatocyte injury such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver. HFE analysis (HFE / Hemochromatosis HFE Gene Analysis, Blood) may be used to confirm the clinical diagnosis of hemochromatosis, to diagnose hemochromatosis in asymptomatic individuals with blood tests showing increased iron stores, or for predictive testing of individuals who have a family history of hemochromatosis. The alleles evaluated by HFE gene analysis are evident in approximately 80% of patients with hemochromatosis; a negative report for HFE gene does not rule-out hemochromatosis. In a patient with negative HFE gene testing, elevated iron status for no other obvious reason, and family history of liver disease, additional evaluation of liver iron concentration is indicated. Diagnosis of hemochromatosis may also be based on biochemical analysis and histologic examination of a liver biopsy.
In this assay, FET / Iron Liver Tissue, results are reported as the hepatic iron index (HII) and dry weight of iron. The HII is considered the "gold standard" for diagnosis of hemochromatosis. This test is appropriate when: -Serum iron is >160 mcg/dL -Transferrin saturation is >55% -Ferritin is >400 ng/mL (males) or >200 ng/mL (females) -HFE gene test is negative for HFE variants See Hereditary Hemochromatosis Algorithm in Special Instructions.

**Useful For:** Diagnosis of hemochromatosis

**Interpretation:** A hepatic iron concentration >10,000 mcg/g dry weight is diagnostic for hemochromatosis. Hepatic iron concentrations >3,000 mcg/g are seen when there is iron overload without cellular injury and cirrhosis. Hepatic iron concentrations greater than the reference range are associated with hemosiderosis, thalassemia, and sideroblastic anemia. Some patients with hepatitis or cirrhosis without significant fibrosis will have hepatic iron concentrations at the top end of normal or just slightly above the normal range. Iron accumulates in the liver normally with aging. The hepatic iron index (HII) normalizes hepatic iron concentration for age. The HII is calculated from the hepatic iron concentration by converting the concentration from mcg/g to mcmol/g dry weight and dividing by years of age. The normal range for HII is <1.0. Patients with homozygous hemochromatosis have HII >1.9. Patients with heterozygous hemochromatosis often have HII ranging from 1.0 to 1.9. Patients with hepatitis and alcoholic cirrhosis usually have HII <1.0, although a small percentage of patients with alcoholic cirrhosis have HII in the range of 1.0 to 1.9. Patients with hemochromatosis who have been successfully treated with phlebotomy will have HII <1.0. Liver specimens collected from patients with cirrhosis containing a high degree of fibrosis have results near the low end of the reference range, even though they will show significant iron staining in hepatocytes. While it is true that iron accumulates in hepatocytes in advanced alcoholic cirrhosis with fibrosis, there are relatively few hepatocytes compared to other inert (fibrotic) tissue, so the quantitative iron determination, which is expressed as mcg of iron per gram of dry weight tissues, yields a low result. Histologic examination of all tissue specimens should be performed to facilitate correct interpretation. When structural heterogeneity is apparent histologically, variation in measured iron should be anticipated. We have observed, in approximately 2% of cases, a high degree of hepatic heterogeneity that makes quantitation highly variable.

**Reference Values:**

**IRON**
- Males: 200-2,400 mcg/g dry weight
- Females: 400-1,600 mcg/g dry weight

**IRON INDEX**
Reference values have not been established for patients that are <13 years of age.
- <1.0 mcmol/g/year (> or =13 years)

**Clinical References:**

**Islet Antigen 2 (IA-2) Antibody, Serum**

**Clinical Information:** Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus for 36 years. In recent years, several autoantigens against which islet antibodies are directed have been identified. These include the tyrosine phosphatase-related islet antigen 2 (IA-2), glutamic acid decarboxylase 65, the zinc transporter ZnT8, and insulin. One or more of these autoantibodies are detected in 96% of patients with type 1 diabetes, and are detectable before clinical onset, as well as in symptomatic individuals. A serological study of 50 type 1 diabetics and 50 control subjects conducted simultaneously across 43 laboratories in 16 countries demonstrated a median sensitivity of 57% and a
median specificity of 99% for IA-2 antibody in type 1 diabetes. Prospective studies in relatives of patients with type 1 diabetes have shown that development of 1 or more islet autoantibodies (including IA-2 antibody) provides an early marker of progression to type 1 diabetes. Autoantibody profiles identifying patients destined to develop type 1 diabetes are usually detectable before age 3. In 1 study of relatives seropositive for IA-2 antibody, the risk of developing type 1 diabetes within 5 years was 65.3%. Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom onset in adulthood, societal obesity, and initial insulin-independence. These patients with "latent autoimmune diabetes in adulthood" may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including IA-2).

**Useful For:** Clinical distinction of type 1 from type 2 diabetes mellitus Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes) Prediction of future need for insulin treatment in adult-onset diabetic patients

**Interpretation:** Seropositivity for IA-2 autoantibody (> 0.02 nmol/L) is supportive of: -A diagnosis of type 1 diabetes -A high risk for future development of diabetes -A current or future need for insulin therapy in patients with diabetes

**Reference Values:**
< or =0.02 nmol/L
Reference values apply to all ages.

**Clinical References:**

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**Islet Cell Cytoplasmic Ab, IgG**

**Reference Values:**
< 1:4

Islet cell antibodies (ICAs) are associated with type 1 diabetes (TID), an autoimmune endocrine disorder. ICAs may be present years before the onset of clinical symptoms. To calculate Juvenile Diabetes Foundation (JDF) units: multiply the titer x 5 (1:8  8 x 5 = 40 JDF Units).

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**Isoagglutinin Titer, Anti-A, Serum**

**Clinical Information:** Isoagglutinins are antibodies produced by an individual that cause agglutination of RBCs in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type B or O individuals will usually possess anti-A. The anti-A is formed in response to exposure to A-like antigenic structures found in ubiquitous non-red cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at 3 to 6 months of age. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia. Some individuals with roundworm infections will have elevated levels of anti-A.

**Useful For:** Evaluation of individuals with possible hypogammaglobulinemia Investigation of suspected roundworm infections

**Interpretation:** The result is reported as antiglobulin phase, in general representing IgG antibody. The
result is the reciprocal of the highest dilution up to 1:2048 at which macroscopic agglutination (1+) is observed. Dilutions >1:2048 are reported as >2048.

Reference Values:
Interpretation depends on clinical setting.


**Isoagglutinin Titer, Anti-B, Serum**

Clinical Information: Isoagglutinins are antibodies produced by an individual that cause agglutination of red blood cells in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type A or O individuals will usually possess anti-B. The anti-B is formed in response to exposure to B-like antigenic structures found in ubiquitous non-red cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at 3 to 6 months of age. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be associated with acquired and congenital hypogammaglobulinemia and agammaglobulinemia.

Useful For: Evaluation of individuals with possible hypogammaglobulinemia Investigation of suspected roundworm infections

Interpretation: The result is reported as antiglobulin phase, in general representing IgG antibody. The result is the reciprocal of the highest dilution up to 1:2048 at which macroscopic agglutination (1+) is observed. Dilutions >1:2048 are reported as >2048.

Reference Values:
Interpretation depends on clinical setting.


**Isocyanate HDI, IgE**

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1 0.35-0.69  Equivocal
2 0.70-3.49  Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive
Reference values apply to all ages.


Isocyanate MDI, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1 0.35-0.69  Equivocal
2 0.70-3.49  Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive

Isocyanate TDI, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Isoniazid, Serum/Plasma

Reference Values:
Usual therapeutic range in the treatment of tuberculosis: 1 - 7 mcg/mL. Toxic symptoms present at
Isovaleryl-CoA Dehydrogenase (IVD) Gene Mutation Analysis (A282V)

**Clinical Information:** Isovaleric acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism associated with germline mutations of the isovaleryl-CoA dehydrogenase (IVD) gene. Mutations in this gene cause isovaleryl-CoA dehydrogenase (IVD) deficiency. This enzyme defect results in the accumulation of derivatives of isovaleryl-CoA, including free isovaleric acid, 3-OH valeric acid, N-isovalerylglycine, and isovalerylcarnitine. Diagnosis relies primarily on the identification of these metabolites in urine by organic acid and acylglycine analyses, and in plasma by acylcarnitine analysis. Patients with IVA may present with various phenotypes, from the acute, neonatal phenotype to the chronic intermittent phenotype. Typically patients present with fairly nonspecific features including poor feeding and vomiting. During these episodes, a characteristic smell of "dirty socks" may be present. In the past, many patients with neonatal onset died during the first episode, while survivors of acute manifestations often suffered neurological sequelae due to incurred central nervous system damage. Therefore, early diagnosis and treatment is of the utmost importance. Newborn screening for IVA was established to allow for early detection by acylcarnitine analysis and presymptomatic initiation of treatment. This early detection has led to improved prognosis for IVA patients. Molecular follow-up testing for patients with positive newborn screening for IVA has led to the identification of specific mutant alleles. One such mutant allele A282V (historic nomenclature:A282V, current nomenclature: A314V) has been found to be overrepresented in patients detected by newborn screening. Clinical evaluation of patients with the A282V mutant allele suggests that this specific mutant allele may confer a milder clinical phenotype. Accordingly, determination of the patient's genotype with respect to the A282V mutation has implications for patient management and genetic counseling.

**Useful For:** Confirmation of clinical or biochemical diagnosis of isovaleric acidemia Providing prognostic information for patients with isovaleric acidemia

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

Ispaghula, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
</table>

Reference values apply to all ages.


**ITCON 81247**

**Itraconazole, Serum**

Clinical Information: Itraconazole is a synthetic triazole antifungal drug approved for treatment and prophylaxis of a variety of fungal infections. Its activity results from inhibition of fungal synthesis of ergosterol, an integral component of fungal cell membranes. Concerns about adequate absorption and drug interactions are some of the major indications for therapeutic drug monitoring. Mean oral bioavailability approximates 55% but is highly variable; absorption can be enhanced by food or acidic drinks. Hepatic enzyme inducers can cause low serum itraconazole levels, and coadministration of these drugs has been associated with itraconazole therapeutic failure. Itraconazole therapeutic efficacy is greatest when serum concentrations exceed 0.5 mcg/mL for localized infections, or 1.0 mcg/mL for systemic infections. An active metabolite, hydroxyitraconazole, is present in serum at roughly twice the level of the parent drug. These concentrations refer to analysis by HPLC; quantitation by bioassay results in considerably higher apparent drug measurements, due to reactivity with the active metabolite.

Useful For: Verifying systemic absorption of orally administered itraconazole The test is indicated in patients with life-threatening fungal infections and in patients considered at risk for poor absorption or rapid clearance of itraconazole.

Interpretation: A lower cutoff concentration has not been defined that applies in all cases. The serum concentration must be interpreted in association with other variables, such as the nature of the infection, the specific microorganism, and minimal inhibitory concentration (MIC) results, if available. Localized infections are more likely to respond when serum itraconazole is >0.5 mcg/mL (by HPLC); systemic infections generally require drug concentrations >1.0 mcg/mL.

Reference Values:

<table>
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<tr>
<th>ITRACONAZOLE (TROUGH)</th>
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<tbody>
<tr>
<td>&gt;0.5 mcg/mL (localized infection)</td>
</tr>
<tr>
<td>&gt;1 mcg/mL (systemic infection)</td>
</tr>
</tbody>
</table>
HYDROXYITRACONAZOLE

No therapeutic range established; activity and serum concentration are similar to parent drug.

**Clinical References:**

**Jack Fruit, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**Jack Mackerel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are...
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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*Reference values apply to all ages.*


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**JAK2 Exon 12 and Other Non-V617F Mutation Detection, Blood**

**Clinical Information:** DNA sequence mutations in the Janus kinase 2 gene (JAK2) are found in the hematopoietic cells of several myeloproliferative neoplasms (MPNs), most frequently polycythemia vera (close to 100%), essential thrombocytopenia (approximately 50%), and primary myelofibrosis (approximately 50%). Mutations in JAK2 have been reported at much lower frequency in other MPNs, chronic myelomonocytic leukemia and mixed MPN/myelodysplastic syndromes, but essentially never in chronic myelogenous leukemia (CML), reactive cytoses, or normal patients. Mutations are believed to cause constitutive activation of the JAK2 protein, which is an intracellular tyrosine kinase important for signal transduction in many hematopoietic cells. Since it is often difficult to distinguish reactive conditions from the non-CML MPNs, identification of a JAK2 mutation has diagnostic value. Potential prognostic significance of JAK2 mutation detection in chronic myeloid disorders has yet to be clearly established. The vast majority of JAK2 mutations occur as base pair 1849 in the gene, resulting in a JAK2 V617F protein change. In all cases being evaluated for JAK2 mutation status, the initial test that should be ordered is JAK2B / JAK2 V617F Mutation Detection, Blood, a sensitive assay for detection of the mutation. However, if no JAK2 V617F mutation is found, further evaluation of JAK2 may be clinically...
indicated. Over 50 different mutations have now been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, research in this area is ongoing. This assay for non-V617F/alternative JAK2 mutations is designed to obtain the sequence for JAK2 exons 12 through the first 90% of exon 15, which spans the region containing all mutations reported to date.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm, particularly when a diagnosis of polycythemia is being entertained. This is a second-order test that should be used when the test for the JAK2B / JAK2 V617F Mutation Detection, Blood test is negative.

**Interpretation:** The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation. If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Interpretation: The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation. If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References:

JAK2 V617F Mutation Detection, Blood

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis, and 50% to 60% of essential thrombocytopenia. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET).(5-9) Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation
-Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.

Clinical References:

JAK2 V617F Mutation Detection, Bone Marrow

Current as of July 8, 2016 11:28 am CDT
Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis (PMF), and 50% to 60% of essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET).(5-9) Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation -Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values: An interpretive report will be provided.


JAK2 V617F Mutation Detection, Varies

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis (PMF), and 50% to 60% of essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET).(5-9) Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation -Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.


Jalapeno/Chipotle (Capsicum annuum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

Japanese Cedar, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
Japanese Millet, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

### JC Polyoma Virus DNA, Quantitative Real-Time PCR, Plasma

**Reference Values:**

Reference Range: \(<500\) copies/mL

### JC Virus (JCV) Detection by In Situ Hybridization

**Clinical Information:** JC virus (JCV) is the etiologic agent of progressive multifocal leukoencephalopathy (PML), a rare, demyelinating, fatal disorder of the central nervous system which occurs on a background of immune deficiency. PML is an infrequent complication of a wide variety of conditions, including lymphoproliferative disorders (Hodgkin disease, chronic lymphocytic leukemia), sarcoidosis, tuberculosis, and immunodeficiency diseases (AIDS).

**Useful For:** Confirming a clinical and histopathologic diagnosis of progressive multifocal leukoencephalopathy (PML)

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation/analysis is needed, please request test 70012 / Pathology Consultation along with this test.

**Clinical References:**

### JC Virus, Molecular Detection, PCR, Spinal Fluid

**Clinical Information:** JC virus (JCV), a member of the genus Polyomavirus, is a small non-enveloped DNA-containing virus. Primary infection occurs in early childhood, with a prevalence of >80%. The virus is latent but can reactivate in immunosuppressed patients, especially those with AIDS. JCV is recognized as the etiologic agent of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system. Histologic examination of brain biopsy tissue may reveal characteristic pathologic changes localized mainly in oligodendrocytes and astrocytes. Detection of JCV DNA by PCR (target gene, large T antigen) in the cerebrospinal fluid specimens of patients with suspected PML infection has replaced the need for biopsy tissue for laboratory diagnosis. Importantly, the PCR test is specific with no cross-reaction with BK virus, a closely related polyomavirus.

**Useful For:** An aid in diagnosing progressive multifocal leukoencephalopathy due to JC virus

**Interpretation:** Detection of JC virus (JCV) DNA supports the clinical diagnosis of progressive multifocal leukoencephalopathy due to JCV.

**Reference Values:** Negative

**Clinical References:**
Jo 1 Antibodies, IgG, Serum

Clinical Information: Jo 1 (histidyl tRNA synthetase) is a member of the amino acyl-tRNA synthetase family of enzymes found in all nucleated cells. Jo 1 antibodies in patients with polymyositis bind to conformational epitopes of the enzyme protein and inhibit its catalytic activity in vitro. Jo 1 antibodies are a marker for the disease polymyositis, and occur most commonly in myositis patients who also have interstitial lung disease. The antibodies occur in up to 50% of patients with interstitial pulmonary fibrosis and symmetrical polyarthritis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

Useful For: Evaluating patients with signs and symptoms compatible with a connective tissue disease, especially those patients with muscle pain and limb weakness, concomitant pulmonary signs and symptoms, Raynaud’s phenomenon, and arthritis.

Interpretation: A positive result for Jo 1 antibodies is consistent with the diagnosis of polymyositis and suggests an increased risk of pulmonary involvement with fibrosis in such patients.

Reference Values:
- <1.0 U (negative)
- ≥1.0 U (positive)


Johnson Grass, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


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**June Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
Juniper Western (Juniperus occidentalis) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Kallmann Syndrome, Xp22.3 Deletion, FISH

**Clinical Information:** This test is appropriate for individuals with clinical features suggestive of Kallmann syndrome and carrier testing for women with a family history of X-linked ichthyosis. Kallmann syndrome is associated with a deletion on the short arm of the X chromosome. The syndrome is an X-linked disease and can be suspected in patients with complete absence of smell (anosmia), hypogonadism, and delayed sexual development. The phenotype may include gynecomastia, bimanual synkinesis (1 hand copying the movements of the other hand), shortened fourth metacarpal bone, and absence of a kidney. Kallmann syndrome affects mainly males, but rare cases of affected females have been reported. FISH studies are highly specific and do not exclude other chromosome abnormalities. For this reason, we recommend that patients suspected of having Kallmann syndrome also have conventional chromosome studies (CMS / Chromosome Analysis, for Congenital Disorders, Blood) performed to rule out other chromosome abnormalities or translocations.

**Useful For:** Establishing a diagnosis of X-linked Kallmann syndrome Detecting cryptic rearrangements involving Xp22.3 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern (2 signals in females and 1 signal in males) in each metaphase is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region on an X chromosome will be reported as having a deletion of the regions tested by this probe. This is consistent with a diagnosis of Kallmann syndrome (Xp22.3 deletion).

**Reference Values:**
An interpretive report will be provided.


Kappa and Lambda Free Light Chains (Bence Jones Protein), Quantitative, Urine

**Reference Values:**
Total Protein: 10-140 mg/d
Albumin, Urine: Detected
Alpha-1, Globulins, Urine: None Detected
Alpha-2, Globulins, Urine: None Detected

Beta Globulins, Urine: None Detected
Gamma, Urine: None Detected
Free Urinary Kappa Light Chains: 0.14-2.42 mg/dL
Free Urinary Kappa Excretion/Day: by report
Free Urinary Lambda Light Chains: 0.02-0.67 mg/dL
Free Urinary Lambda Excretion/Day: by report
Free Urinary Kappa/Lambda Ratio: 2.04-10.37 (ratio)
IFE Interpretation: by report

Test Information: Total Protein
Total urinary protein is determined nephelometrically by adding the albumin and Kappa and/or Lambda light chains. This value may not agree with the total protein as determined by chemical methods, which characteristically underestimate urinary light chains.

**KETAX**

**Ketamine and Metabolite Confirmation, Chain of Custody, Urine**

**Clinical Information:** Ketamine has been used in the United States as an anesthetic induction agent since 1972. The drug acts by noncompetitive antagonism of the N-methyl-D-aspartate (NMDA)-type glutamate receptors. Ketamine has become a popular street drug because of its hallucinogenic effects. Ketamine has a half-life of 3 to 4 hours, and is metabolized to norketamine. The effects from ketamine last from 1 to 5 hours, and ketamine and/or norketamine can be detected in the urine for a period of 1 to 2 days following use. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and confirmation of ketamine use Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of ketamine and/or norketamine >25 ng/mL is a strong indicator that the patient has used ketamine.

**Reference Values:**
Negative

**Clinical References:**

**KETAU**

**Ketamine and Metabolite Confirmation, Urine**

**Clinical Information:** Ketamine has been used in the United States as an anesthetic induction agent since 1972. The drug acts by noncompetitive antagonism of the N-methyl-D-aspartate (NMDA)-type glutamate receptors. Ketamine has become a popular street drug because of its hallucinogenic effects. Ketamine has a half-life of 3 to 4 hours, and is metabolized to norketamine. The effects from ketamine last from 1 to 5 hours, and ketamine and/or norketamine can be detected in the urine for a period of 1 to 2 days following use.

**Useful For:** Detection and confirmation of ketamine use

**Interpretation:** The presence of ketamine and/or norketamine >25 ng/mL is a strong indicator that the patient has used ketamine.
The patient has used ketamine.

**Reference Values:**
Negative


**FKMS 57857**

**Ketamine and Metabolite Screen, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis
Units: ng/mL

Ketamine:
- **Synonyms:** Ketalar
- **Reported levels during anesthesia:** 500–6500 ng/mL

Norketamine:
- **Synonyms:** Ketamine Metabolite

The intravenous administration of 2 mg/kg of Ketamine followed by continuous infusion of 41 mcg/kg/minute produced an average steady-state plasma concentration of 2200 ng Ketamine/mL and an average peak Norketamine level of 1050 ng/mL which occurred near the end of the 3 hour infusion.

**FKETO 90317**

**Ketoconazole, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Peak plasma levels of 5.4 +/- 1.7 mcg/mL occurred at approximately 1 hour following a single 200 mg dose and peak plasma levels of 22 +/- 3 mcg/mL occurred at approximately 2 hours following a single 800 mg dose of ketoconazole.

**89027**

**Ki-67(MIB-1), Breast, Quantitative Immunohistochemistry, Automated**

**Clinical Information:** Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with breast carcinoma

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and...
Pathology, Mayo Clinic (see Method Description).

**Reference Values:**
Varies by tumor type; values reported from 0% to 100%


Kidney Bean (Red), IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>


Kidney Stone Analysis

**Clinical Information:** The composition of urinary stones may vary from a simple crystal to a...
complex mixture containing several different species of crystals. The composition of the nidus (center) may be entirely different from that of the peripheral layers. Eighty percent of patients with kidney stones have a history of recurrent stone formation. Knowledge of stone composition is necessary to guide therapy of patients with recurrent stone formation. Treatment of urinary calculi is complex.(1) In an overly simplified format, the following patterns are often treated as follows: -Hyperuricuria and predominately uric acid stones: alkalize urine to increase uric acid solubility. -Hypercalcuiuria and predominately hydroxyapatite stones: acidify urine to increase calcium solubility. However, treatment also depends on urine pH and urine phosphate, sulfate, oxalate, and citrate concentrations. -Hyperoxaluria and calcium oxalate stones: increase daily fluid intake and consider reduction of daily calcium. However, daily requirements for calcium to maintain good bone formation complicate the treatment. -Magnesium ammonium phosphate stones (struvite): Investigate and treat urinary tract infection. See Kidney Stones and Stone Analysis in Publications.

**Useful For:** Managing patients with recurrent renal calculi

**Interpretation:** The interpretation of stone analysis results is complex, and beyond the scope of this text. We refer you to chapter 25 of Smith LH: Diseases of the Kidney. Vol 1. Fourth edition. Edited by RW Schrier, CW Gottschalk. Boston, MA, Little, Brown and Company, 1987. Calcium oxalate stones: -Production of calcium oxalate stones consisting of oxalate dihydrate indicate that the stone is newly formed and current urine constituents can be used to assess the importance of supersaturation. -Production of calcium oxalate stones consisting of oxalate monohydrate indicate an old (>2 months since formed) stone and current urine composition may not be meaningful. Magnesium ammonium phosphate stones (struvite): -Production of magnesium ammonium phosphate stones (struvite) indicates that the cause of stone formation was infection. -Treatment of the infection is the only way to inhibit further stone formation. Ephedrine/guaifenesin stones: -Certain herbal and over-the-counter preparations (eg, Mah Jung) contain high levels of ephedrine and guaifenesin. Excessive consumption of these products can lead to the formation of ephedrine/guaifenesin stones.

**Reference Values:**
Quantitative report


**KIT Asp816Val Mutation Analysis, Blood**

**Clinical Information:** Systemic mastocytosis is a hematopoietic neoplasm that can be included in the general category of chronic myeloproliferative disorders (CMPDs). These neoplasms are characterized by excessive proliferation of 1 or more myeloid lineages, with cells filling the bone marrow and populating other hematopoietic sites. In systemic mastocytosis, mast cell proliferation is the defining feature, although other myeloid lineages and B cells are frequently part of the neoplastic clone. Function-altering point mutations in KIT, a gene coding for a membrane receptor tyrosine kinase, have been found in myeloid lineage cells in the majority of systemic mastocytosis cases. The most common KIT mutation is an adenine to thymine base substitution (A->T) at nucleotide position 2468, which results in an aspartic acid to valine change in the protein (Asp816Val). Much less frequently, other mutations at this same location are found and occasional cases with mutations at other locations have also been reported. Mutations at the 816 codon are believed to alter the protein such that it is in a constitutively activated state. The main downstream effect of KIT activation is cell proliferation. Detection of a mutation at the 816 codon is included as 1 of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib, a drug commonly used to treat CMPDs. It is now clear that individual mast cell neoplasms are variable with respect to the number of cell lineages containing the mutation; some having positivity only in mast cells and others having positivity in additional myeloid and even lymphoid lineages. The mutation has not been reported in normal tissues.
Useful For: Diagnosing systemic mastocytosis

Interpretation: The test will be interpreted as positive or negative for KIT Asp816Val.

Reference Values:
An interpretive report will be provided indicating the mutation status as positive or negative.

Clinical References:

KITAS
88802

KIT Asp816Val Mutation Analysis, Qualitative PCR

Clinical Information: Systemic mastocytosis is a hematopoietic neoplasm that can be included in the general category of chronic myeloproliferative disorders (CMPDs). These neoplasms are characterized by excessive proliferation of 1 or more myeloid lineages, with cells filling the bone marrow and populating other hematopoietic sites. In systemic mastocytosis, mast cell proliferation is the defining feature, although other myeloid lineages and B-cells are frequently part of the neoplastic clone. Function-altering point mutations in KIT, a gene coding for a membrane receptor tyrosine kinase, have been found in myeloid lineage cells in the majority of systemic mastocytosis cases. The most common KIT mutation is an adenine-to-thymine base substitution (A->T) at nucleotide position 2468, which results in an aspartic acid-to-valine change in the protein (Asp816Val). Much less frequently, other mutations at this same location are found and occasional cases with mutations at other locations have also been reported. Mutations at the 816 codon are believed to alter the protein such that it is in a constitutively activated state. The main downstream effect of KIT activation is cell proliferation. Detection of a mutation at the 816 codon is included as 1 of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib, a drug commonly used to treat CMPDs. It is now clear that individual mast cell neoplasms are variable with respect to the number of cell lineages containing the mutation; some having positivity only in mast cells and others having positivity in additional myeloid and even lymphoid lineages. The mutation has not been reported in normal tissues.

Useful For: Diagnosing systemic mastocytosis

Interpretation: The test will be interpreted as positive or negative for KIT Asp816Val.

Reference Values:
An interpretive report will be provided indicating the mutation status as positive or negative.

Clinical References:

KITBM
61745

KIT Asp816Val Mutation Analysis, Qualitative PCR, Bone Marrow

Clinical Information: Systemic mastocytosis is a hematopoietic neoplasm that can be included in the general category of chronic myeloproliferative disorders (CMPDs). These neoplasms are characterized by excessive proliferation of 1 or more myeloid lineages, with cells filling the bone marrow and populating...
other hematopoietic sites. In systemic mastocytosis, mast cell proliferation is the defining feature, although other myeloid lineages and B cells are frequently part of the neoplastic clone. Function-altering point mutations in KIT, a gene coding for a membrane receptor tyrosine kinase, have been found in myeloid lineage cells in the majority of systemic mastocytosis cases. The most common KIT mutation is an adenine to thymine base substitution (A->T) at nucleotide position 2468, which results in an aspartic acid to valine change in the protein (Asp816Val). Much less frequently, other mutations at this same location are found and occasional cases with mutations at other locations have also been reported. Mutations at the 816 codon are believed to alter the protein such that it is in a constitutively activated state. The main downstream effect of KIT activation is cell proliferation. Detection of a mutation at the 816 codon is included as 1 of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib, a drug commonly used to treat CMPDs. It is now clear that individual mast cell neoplasms are variable with respect to the number of cell lineages containing the mutation; some having positivity only in mast cells and others having positivity in additional myeloid and even lymphoid lineages. The mutation has not been reported in normal tissues.

**Useful For:** Diagnosing systemic mastocytosis

**Interpretation:** The test will be interpreted as positive or negative for KIT Asp816Val.

**Reference Values:**
An interpretive report will be provided indicating the mutation status as positive or negative.


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**KIT11**

**KIT Exon 11, Mutation Analysis**

**Clinical Information:** Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or melanomas Identification of a mutation in exon 11 of the KIT gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.

KIT Exon 13, Mutation Analysis

Clinical Information: Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

Useful For: Diagnosis and management of patients with gastrointestinal stromal tumors or melanomas

Identification of a mutation in exon 13 of the KIT gene

Interpretation: Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

Reference Values:
An interpretative report will be provided.

Clinical References:

KIT Exon 17, Mutation Analysis

Clinical Information: Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

Useful For: Diagnosis and management of patients with gastrointestinal stromal tumors or melanomas

Identification of a mutation in exon 17 of the KIT

Interpretation: Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

Reference Values:
An interpretative report will be provided.

Clinical References:

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**KIT Exon 8, Mutation Analysis**

**Clinical Information:** Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 8 of the KIT gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.


**KIT Exon 9, Mutation Analysis**

**Clinical Information:** Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors, mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 9 of the KIT gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.


**KIT**

**KIT Mutation Exons 8-11 and 17, Hematologic Neoplasms, Sequencing**

**Clinical Information:** Acquired mutations in the KIT gene are identified in a subset of acute myeloid leukemias (AML) characterized by inv16 or t(16;16) CBFB-MYH11 or t(8;21) RUNX1-RUNX1T1 genetic abnormalities (approximately 10%-20% of cases) and in this setting, the additional presence of KIT gene mutation has been described as an adverse prognostic factor in some studies. KIT mutations in AML tend to involve exons 8 through 11 and 17, although the p.Asp816Val (D816V) variant that is highly prevalent in systemic mastocytosis is less common in AML. Mastocytosis is a hematologic disorder characterized by abnormal mast cell expansion in the bone marrow and extramedullary organ sites (eg, skin, gastrointestinal tract). Disease can be localized to skin (ie, cutaneous mastocytosis) or present systemically, with variable features of disease aggressiveness and symptomatology. Mutations in the KIT gene are identified in a large majority of patients with both cutaneous mastocytosis (CM) and systemic mastocytosis (SM). The D816V abnormality is identified in most patients with SM and this finding represents an important minor diagnostic criterion in the 2008 WHO classification. The D816V is less commonly seen in CM, although single nucleotide variants are present in other KIT exons. Rare cases of familial mastocytosis are also described with KIT mutations involving exons 8 and 9. Although KIT gene mutation represents an important diagnostic marker for SM, the number of bone marrow mast cells is often limited in aspirate samples. Therefore, if SM is clinically and pathologically suspected, KIT testing should first proceed with a sensitive and specific screen for the D816V (KITB / KIT Asp816Val Mutation Analysis, Blood; KITBM / KIT Asp816Val Mutation Analysis, Qualitative PCR, Bone Marrow; or KITAS / KIT Asp816Val Mutation Analysis, Qualitative PCR) prior to consideration of KIT gene sequencing, based on the greatly enhanced sensitivity of the PCR test for this particular variant. In AML, KIT sequencing is preferred, given the wider spectrum of mutations in other KIT exons.

**Useful For:** The prognostic assessment of acute myeloid leukemias with core binding factor translocations (inv16 or t(16;16) CBFB-MYH11 or t(8;21) RUNX1-RUNX1T1) and to help establish the diagnosis in some cases of mastocytosis

**Interpretation:** Mutations detected or not detected. An interpretive report will be issued.

**Reference Values:**
An interpretive report will be provided

Kiwi Fruit, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; 50 or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
<td></td>
</tr>
</tbody>
</table>


Known 45,X, Mosaicism Reflex Analysis, FISH

Clinical Information: This test is appropriate for use in individuals with a karyotype of 45, X. Ullrich-Turner syndrome (UTS), also called Turner syndrome, is a genetic disorder associated with the apparent loss of a sex chromosome. Routine cytogenetic methods have identified 3 types of chromosomal abnormalities in UTS patients: loss of an entire X chromosome (45,X), structural X chromosome abnormalities, and mosaicism with an X or Y abnormality. In mosaicism, 2 or more populations of cells with different karyotypes are present (eg, 45,X/46,XX). The incidence of UTS is approximately 1 in 3,000 newborn girls. Many of these patients demonstrate the 45,X karyotype. About 30% to 50% are mosaic, with either a 45,X/46,XX karyotype or a structurally abnormal X chromosome. Fewer than 15% of patients with UTS appear to have mosaicism with a 46,XY cell population or a Y chromosome rearrangement. Identifying the mosaic status of patients with UTS is of clinical importance because phenotypic expression and clinical management are dependent upon the karyotype result. Patients with a
Y chromosome have a 15% to 25% increased risk of gonadoblastoma. Failure to identify an XY signal pattern does not rule out the possibility of <0.6% Y chromosome mosaicism.

**Useful For:** Detecting sex chromosome mosaicism in patients with a 45,X karyotype

**Interpretation:** An XX clone is confirmed when > or =1.0% cells display with 2 X chromosome signals. An XY clone is confirmed when > or =0.6% cells display a 1 X and 1 Y signal pattern. Females with a 45,X/46,XX karyotype have no increased risk of gonadoblastoma and generally have a more moderate expression of Turner syndrome features than females with a nonmosaic 45,X karyotype. The presence of a Y chromosome confers increased risk of gonadoblastoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**KPC (blaKPC) and NDM (blaNDM) in Gram-Negative Bacilli, Molecular Detection, PCR**

**Clinical Information:** Nonsusceptibility to carbapenems in gram-negative bacilli by means of the enzyme KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) is becoming more common. The genes blaKPC and blaNDM encode KPC and NDM enzyme production, respectively. In addition to KPC and NDM production, there are other mechanisms of resistance to carbapenems in gram-negative bacilli, including production of other carbapenemases, or plasmid-encoded AmpC, or extended beta-lactamase production combined with decreased membrane permeability. Detection of carbapenemases by the modified Hodge test may be subjective and is not rapid. Testing for the minimum inhibitory concentration (MIC) determines the level but not the mechanism of resistance. PCR is a sensitive, specific, and rapid means of detecting of a specific portion of the genes encoding KPC and NDM production.

**Useful For:** Assessing pure isolates of gram-negative bacilli for mechanism of carbapenem resistance

**Interpretation:** This PCR detects and differentiates both blaKPC and blaNDM. A positive KPC (Klebsiella pneumoniae carbapenemase) PCR indicates that the isolate carries blaKPC. A positive NDM (New Delhi metallo-beta-lactamase) PCR indicates the isolate carries blaNDM. A negative result indicates the absence of detectable blaKPC or blaNDM DNA; however, false-negative results may occur due to inhibition of PCR, sequence variability underlying primers and, or loss of a plasmid carrying blaKPC and blaNDM.

**Reference Values:**
Not applicable

**Clinical References:**
surveillance to detect unrecognized colonized patients who may be a potential source for carbapenemase-resistant Enterobacteriaceae (CRE) transmission. Such surveillance testing may be focused in certain high-risk settings or patient groups (e.g., ICUs, long-term acute care, patients transferred from areas or facilities with high CRE prevalence) or by infection control to investigate an outbreak. Nonsusceptibility to carbapenems in gram-negative bacilli by means of the enzyme KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) is becoming more common. The genes blaKPC and blaNDM encode KPC and NDM enzyme production, respectively. PCR is a sensitive, specific, and rapid means identifying patients colonized by CRE harboring blaKPC or blaNDM.

**Useful For:** Identifying carriers of carbapenem-resistant Enterobacteriaceae harboring KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) genes

**Interpretation:** This PCR detects and differentiates blaKPC and blaNDM in surveillance specimens (perirectal/rectal swabs or stool). A positive KPC (Klebsiella pneumoniae carbapenemase) and/or NDM (New Delhi metallo-beta-lactamase) PCR indicates that the patient is colonized by carbapenemase-resistant Enterobacteriaceae harboring blaKPC and/or blaNDM, respectively. A negative result indicates the absence of detectable DNA; however, false-negative results may occur due to inhibition of PCR, sequence variability underlying primers and probes, or the presence of the blaKPC or blaNDM genes in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

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**KPND1**

**KPC and NDM PCR (Bill Only)**

**Reference Values:**
This test is for Billing Purposes Only.
This is not an orderable test.

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**KRABZ**

**Krabbe Disease, Full Gene Analysis and Large (30 kb) Deletion, PCR**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). GALC is encoded by the GALC gene located on 14q31. Krabbe disease occurs in approximately 1 in 100,000 live births with a carrier frequency of about 1 in 150 in the general population. Deficiency of GALC activity leads to an accumulation of galactosylceramide in globoid cells (multinucleated macrophages) causing severe demyelination throughout the brain. The toxic metabolite galactosylsphingosine (psychosine), an apoptotic compound, accumulates in oligodendrocytes and Schwann cells and contributes to disease pathogenicity. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration follows with death usually occurring by age 13 months. There are later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. The clinical course of Krabbe disease can be variable even within the same family. Treatment is mostly...
supportive, although hematopoietic stem cell transplantation has shown some success if treatment begins before neurologic damage has occurred. The recommended first-tier test for Krabbe disease is LDSBS / Lysosomal Disorders Screen, Blood Spot, CBGC / Galactosylceramide Beta-Galactosidase, Leukocytes, or CBGT / Galactosylceramide Beta-Galactosidase, Fibroblasts. Individuals with GALC activity below the reference range for these assays are more likely to have mutations in the GALC gene that are identifiable by molecular genetic testing. The above tests are not reliable for detection of carriers of Krabbe disease. Molecular genetic testing (this test) is the recommended test for individuals with a family history of Krabbe disease in which the mutations in the family are unknown. Molecular tests form the basis of confirmatory or carrier testing. This assay includes DNA sequencing of all 17 exons within the GALC gene as well as evaluation for the common 30-kb deletion spanning intron 10 through the end of the gene. This deletion accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second GALC mutation (with the exception of late-onset mutations) are predicted to have infantile Krabbe disease. The c.857G>A (p.Gly286Asp) mutation, on the other hand, is only associated with a late-onset phenotype.

**Useful For:** Second-tier test for confirming a diagnosis of Krabbe disease Carrier testing for individuals with a family history of Krabbe disease in the absence of known mutations in the family

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**KRAS**

**KRAS Gene, Known Mutation, Blood**

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be underestimated. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and multiple lentigines (LEOPARD: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-mitogen-activated protein kinase (MAPK) pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals. Mutations in RAF1
are identified in approximately 3% to 17%, SOS1 in approximately 10%, and KRAS in <5% of affected
individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized
in up to 30% to 75% of families. The KRAS gene has been shown to have a total of 6 exons that are
alternatively spliced into K-Ras isoforms A and B. Exon 1 is noncoding. Exons 2, 3, and 4 are invariant
coding exons, whereas exon 5 undergoes alternative splicing. K-Ras isoform B results from exon 5
skipping. In K-Ras isoform A mRNA, exon 6 encodes the 3-prime untranslated region, whereas in K-Ras
isoform B mRNA, exon 6 encodes the C-terminal region. Reported mutations in KRAS associated with
NS are missense mutations. It has been proposed that all reported mutations lead to stabilization of K-Ras
in the active conformation, most likely by different gain of function mechanisms. Mutations in KRAS
have been identified in individuals with other disorders that overlap phenotypically with NS, including
CFC syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like
facial features, and severe psychomotor developmental delay. KRAS mutations have also been associated
with Costello syndrome (CS), which is characterized by coarse facies, short stature, distinctive hand
posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental
disability. Genetic testing for KRAS mutations can allow for the confirmation of a suspected genetic
disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management
of the disease and preconception, prenatal, and family counseling.

**Useful For:** Genetic testing for individuals at risk for a known KRAS mutation

**Interpretation:** All detected alterations will be evaluated according to American College of Medical
Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known,
predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or
known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
genotypic and phenotypic spectrum in patients with KRAS germline mutations. J Med Genet
due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationship and overlap
   Metab 2011 Feb;25(1):161-179

**KRAS Mutation Analysis, 7 Mutation Panel, Colorectal**

**Clinical Information:** Colorectal cancer is currently among the most common malignancies
diagnosed each year. Strategies that focus on early detection and prevention effectively decrease the risk
of mortality associated with the disease. In addition, an increase in survival rate for individuals with
advanced stage colorectal cancer has been observed as a result of advancements in standard
chemotherapeutic agents and the development of specialized targeted therapies. Monoclonal antibodies
against epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, represent a new
area of targeted therapy for such patients. However, studies have shown that not all individuals with
colorectal cancer respond to EGFR-targeted molecules. Because the combination of targeted therapy and
standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the
individuals most likely to benefit from such targeted therapies are desirable. EGFR is a growth factor
receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in
activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately
regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK
pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit
activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with colorectal cancer. One of the most common somatic alterations in colon cancer is the presence of activating mutations in the proto-oncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because mutant KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents such as cetuximab and panitumumab, which prevent ligand-binding to EGFR, do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of mutant KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in colon cancer is confined to patients with tumors lacking KRAS mutations. As a result, the mutation status of KRAS can be a useful marker by which patients are selected for EGFR-targeted therapy. At this time, this test is approved specifically for colorectal tumors and metastatic lesions from a colorectal primary. Please refer to KRASO / KRAS Mutation Analysis, 7 Mutation Panel, Other (Non-Colorectal) for KRAS testing in noncolorectal tumors.

**Useful For:** Prognostic markers for cancer patients treated with epidermal growth factor receptor-targeted therapies

**Interpretation:** An interpretative report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**KRASO 35468**

**KRAS Mutation Analysis, 7 Mutation Panel, Other (Non-Colorectal)**

**Clinical Information:** Lung cancer is the leading cause of cancer-related deaths in the world. Non-small cell lung cancer (NSCLC) represents 70% to 85% of all lung cancer diagnoses. Randomized trials have suggested that targeted agents alone or combined with chemotherapy may be beneficial. Because the addition of targeted therapy may lead to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from targeted therapies are desirable. Monoclonal antibodies against epidermal growth factor receptor (EGFR) represent a new area of targeted therapy for such patients. However, studies have shown that not all individuals with NSCLC respond to these EGFR-targeted molecules. EGFR is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success in treating a subset of patients with NSCLC. In NSCLC, one of the most frequently reported alterations in the EGFR-signaling pathway is the presence of a mutation in the proto-oncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because mutant KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents that prevent ligand-binding to EGFR do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of mutant KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors lacking KRAS mutations. As a result, the mutation status of KRAS can be a useful marker by which patients are selected for EGFR-targeted therapy. At this time, this test is for unknown and/or unidentified primary tumors, primary tumors other than colorectal, and metastatic lesions from a primary other than colorectal. Please refer to KRASC / KRAS Mutation Analysis, 7 Mutation Panel, Colorectal for KRAS testing in colorectal tumors.

**Useful For:** Prognostic marker for cancer patients with noncolorectal tumors treated with epidermal growth factor receptor-targeted therapies
**Interpretation:** An interpretative report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**KRAS**

**KRAS, Full Gene Sequence, Blood**

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and multiple lentigines (LEOPARD: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-mitogen-activated protein kinase (MAPK) pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 in approximately 10%, and KRAS in less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in up to 30% to 75% of families. The KRAS gene has been shown to have a total of 6 exons that are alternatively spliced into K-Ras isoforms A and B. Exon 1 is noncoding. Exons 2, 3, and 4 are invariant coding exons, whereas exon 5 undergoes alternative splicing. K-Ras isoform B results from exon 5 skipping. In K-Ras isoform A mRNA, exon 6 encodes the 3-prime untranslated region, whereas in K-Ras isoform B mRNA, exon 6 encodes the C-terminal region. Reported mutations in KRAS associated with NS are missense mutations. It has been proposed that all reported mutations lead to stabilization of K-Ras in the active conformation, most likely by different gain of function mechanisms. Mutations in KRAS have been identified in individuals with other disorders that overlap phenotypically with NS, including CFC syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. KRAS mutations have also been associated with Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability. Genetic testing for KRAS mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Aiding in the diagnosis of KRAS-associated Noonan syndrome, cardiofaciocutaneous syndrome, and Costello syndrome

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or
known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**LACO 62905**

**Lacosamide, Serum**

**Clinical Information:** Lacosamide is approved for adjunctive therapy to treat partial-onset seizures in epileptic patients 17 years of age and older. In clinical trials, the most common side effects were dizziness, headache, nausea, and double vision. Lacosamide is completely absorbed after oral administration with negligible first-pass metabolism. Peak plasma concentrations occur 1 to 4 hours after oral dosing, and the elimination half-life is approximately 13 hours. Steady-state plasma concentrations are achieved after 3 days of twice daily repeated administration. About 40% of the administered dose is eliminated by the renal system unchanged and 30% is metabolized by hepatic isoenzymes (CYP2C9, CYP2C19, and CYP3A4) to the O-desmethyl inactive metabolite. The relationship between lacosamide plasma concentrations and its efficacy or adverse effects is not well established. However, central nervous system toxicity has been associated with higher drug concentrations in plasma.

**Useful For:** Monitoring serum concentrations of lacosamide to ensure compliance and appropriate dosing in specific clinical conditions (ie, severe renal impairment, mild-to-moderate hepatic impairment, and end-stage renal disease)

**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response or adverse effects, particularly when lacosamide is coadministered with other anticonvulsant drugs. Toxic ranges have not been established.

**Reference Values:**
Patients receiving therapeutic doses usually have lacosamide concentrations of 1.0-10.0 mcg/mL.

**Clinical References:**

**LD I 8679**

**Lactate Dehydrogenase (LD) Isoenzymes, Serum**

Current as of July 8, 2016 11:28 am CDT
**Clinical Information:** Total Lactate Dehydrogenase (LD): LD activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. As with other proteins used as tissue-function markers, the appearance of LD in the serum occurs only after prolonged hypoxia and is elevated in a number of clinical conditions including cardiorespiratory diseases, malignancy, hemolysis, and disorders of the liver, kidneys, lung, and muscle. Isoenzymes: LD is a tetrameric cytoplasmic enzyme, composed of H and M subunits. The most usual designation of the isoenzyme is LD-I (H4), LD-II (H3M), LD-III (H2M2), LD-IV (HM3), and LD-V (M4). Tissue specificity is derived from the fact that there is tissue-specific synthesis of subunits in well-defined ratios. Most notably, heart muscle cells preferentially synthesize H subunits, while liver cells synthesize M subunits nearly exclusively. Skeletal muscle also synthesizes largely M subunits so that LD-V is both a liver and skeletal muscle form of LD. The LD-I and LD-V forms are most often used to indicate heart or liver pathology, respectively. LD-I appears elevated in the serum about 24 to 48 hours after a myocardial infarction (MI), but is generally not as useful as troponin or creatine kinase-MB (CK-MB) for detection of MI, unless the MI occurred at least 24 hours prior to testing. Normally, LD-II is greater than LD-I; however, when a MI has occurred, there is a "flip" in the usual ratio of LD-I/LD-II from <1 to >1 (or at least >0.9). Use of the ratio for evaluation of patients with possible cardiovascular injury has largely been replaced by TPNT / Troponin T, Serum. The LD-V form is pronounced in patients with either primary liver disease or liver hypoxia secondary to decreased perfusion, such as occurs following an MI. However, LD-V is usually not as reliable as the transaminases (eg, aspartate aminotransferase, alanine aminotransferase) for evaluating liver function. LD-V also may be elevated in muscular damage and diseases of the skin. Although it does not appear to cause or be associated with any symptoms or particular diseases, the presence of macro-LD (LD combined with an immunoglobulin) can cause an idiosyncratic elevation of total LD.

**Useful For:** Investigating a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood Differentiating heart-synthesized lactate dehydrogenase (LD) from liver and other sources As an aid in the diagnosis of myocardial infarction when used in combination with total creatine kinase (CK) and CK-MB Investigating unexplained causes of LD elevations Detection of macro-LD

**Interpretation:** Marked elevations in lactate dehydrogenase (LD) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate-to-slight increases in LD levels are seen in myocardial infarction (MI), pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and renal disease. In liver disease, elevations of LD are not as great as the increases in aspartate aminotransferase and alanine aminotransferase. Increased levels of the enzyme are found in about one-third of patients with renal disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of renal disease. On occasion, a raised LD level may be the only evidence to suggest the presence of a hidden pulmonary embolus. Isoenzymes: LD-II is found in myocardium. Following a severe MI, the diagnostic ratio of LD-I divided by LD-II will change from <0.9 to >0.9. This is referred to as an LD "flip". LD-I elevation not due to myocardial damage may indicate hemolytic disease or other forms of in vivo hemolysis. Elevation of LD-V (least mobile isoenzyme) usually denotes liver damage. It is rarely helpful in defining skeletal muscle disease. Macro-LD can occur, which results in an elevation of LD for no clinical reason. Macro-LD greatly affects the migration of LD isoenzymes since the addition of an immunoglobulin molecule greatly retards the migration of the usual LD isoenzymes. If macro-LD is present, the electrophoretogram will show atypically migrating isoenzymes with LD activity localized near the origin.

**Reference Values:**

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<tr>
<td>31 days-11 months: 180-435 U/L</td>
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<td>16-17 years: 105-233 U/L</td>
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<tr>
<td>&gt; or =18 years: 122-222 U/L</td>
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Current as of July 8, 2016 11:28 am CDT    800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com   Page 1182
LDBF
8022
Lactate Dehydrogenase (LD), Body Fluid

Reference Values:
Not applicable

LD
8344
Lactate Dehydrogenase (LD), Serum

Clinical Information: Lactate dehydrogenase (LD) activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. Serum LD is elevated in a number of clinical conditions.

Useful For: Investigation of a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood. Monitoring changes in tumor burden after chemotherapy, although, lactate dehydrogenase elevations in patients with cancer are too erratic to be of use in the diagnosis of cancer.

Interpretation: Marked elevations in lactate dehydrogenase (LD) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin’s disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate to slight increases in LD levels are seen in myocardial infarction (MI), pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and renal disease. In liver disease, elevations of LD are not as great as the increases in aspartate amino transferase (AST) and alanine aminotransferase (ALT). Increased levels of the enzyme are found in about one third of patients with renal disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of renal disease. On occasion a raised LD level may be the only evidence to suggest the presence of a hidden pulmonary embolus.

Reference Values:
1-30 days: 135-750 U/L
31 days-11 months: 180-435 U/L
1-3 years: 160-370 U/L
4-6 years: 145-345 U/L
7-9 years: 143-290 U/L
10-12 years: 120-293 U/L
13-15 years: 110-283 U/L
16-17 years: 105-233 U/L
> or =18 years: 122-222 U/L


LACTD
82051
Lactate Dehydrogenase Stain (Bill Only)

Reference Values:
This test is for billing purposes only.

This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**LABF 8030**

**Lactate, Body Fluid**

**Clinical Information:** Lactate found in cerebrospinal fluid (CSF) is predominantly produced by central nervous system (CNS) glycolysis and is independent of serum lactate. Increased CSF lactate concentrations are related to increased cerebral glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism. Lactate measurement in CSF has been proposed as a test to differentiate bacterial from viral meningitis.

**Useful For:** Aid in differentiating between bacterial and viral meningitis Aid in identifying increased glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism

**Interpretation:** Published studies suggest normal cerebrospinal fluid (CSF) lactate concentration is 1.1 to 2.3 mmol/L and meta-analysis of 33 studies concluded concentrations >3.9 mmol/L are suggestive of bacterial meningitis, with lower concentrations suggestive of viral meningitis.

**Reference Values:**
Not applicable


**LAA 8665**

**Lactate, Plasma**

**Clinical Information:** Lactate is the end product of anaerobic carbohydrate metabolism. Major sites of production are skeletal muscle, brain, and erythrocytes. Lactate is metabolized by the liver. The concentration of lactate depends on the rate of production and the rate of liver clearance. The liver can adequately clear lactate until the concentration reaches approximately 2 mmol/L. When this level is exceeded, lactate begins to accumulate rapidly. For example, while resting lactate levels are usually <1 mmol/L, during strenuous exercise levels can rise >20 mmol/L within a few seconds. Lactic acidosis signals the deterioration of the cellular oxidative process and is associated with hyperpnea, weakness, fatigue, stupor, and finally coma. These conditions may be irreversible, even after treatment is administered. Lactate acidosis may be associated with hypoxic conditions (eg, shock, hypovolemia, heart failure, pulmonary insufficiency), metabolic disorders (eg, diabetic ketoacidosis, malignancies), and toxin exposures (eg, ethanol, methanol, salicylates).

**Useful For:** Diagnosing and monitoring patients with lactic acidosis

**Interpretation:** While no definitive concentration of lactate has been established for the diagnosis of lactic acidosis, lactate concentrations exceeding 5 mmol/L and pH <7.25 are generally considered indicative of significant lactic acidosis.

**Reference Values:**
< or =2 years: 0.6-3.2 mmol/L
>2 years: 0.6-2.3 mmol/L

**Lactoferrin, Fecal by ELISA**

**Interpretation:** A positive result is indicative of the presence of lactoferrin, a marker for fecal leukocytes. A negative result does not exclude the presence of intestinal inflammation.

**Reference Values:**
Negative

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**Ladybeetle Multicolored Asian (Harmonia axyridis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 Positive 4 17.50 - 49.99 Strong Positive 5 50.00 - 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Lamb’s Quarter, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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<td>3.50 - 17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5 - 49.9</td>
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Reference values apply to all ages.
Lamb, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Lamellar Body Count Reflex, Amniotic Fluid

Clinical Information: Fetal lung maturity testing is used to determine the risk for developing respiratory distress syndrome (RDS) in infants born prematurely (32-39 weeks). The risk for developing RDS is inversely related to gestational age and is the most common cause of respiratory failure in neonates. RDS is associated with preterm birth due to insufficient production of pulmonary surfactant. Pulmonary surfactant is synthesized by type II pneumocytes. Surfactant consists of 90% phospholipids (primarily phosphatidylcholine and phosphatidylglycerol) and 10% proteins (surfactant proteins [SP]-A,
SP-B, SP-C). Surfactant is packaged into lamellar bodies and is excreted into the alveolar space where it unravels and forms a monolayer on alveolar surfaces. Lamellar bodies can also pass into the amniotic cavity and, hence, are found in amniotic fluid. The surfactant functions to reduce the surface tension in the alveoli, preventing atelectasis. When surfactant is deficient, the small alveoli collapse and the large alveoli become overinflated and stiff, which has been associated with increased risk of developing respiratory distress. The status of fetal lung maturity is reflected in the concentration of surfactant in the form of phospholipids (see FLP / Fetal Lung Profile, Amniotic Fluid) and lamellar bodies present in amniotic fluid. Lamellar bodies are similar in size to platelets and can be quantified on a hematology analyzer utilizing the platelet channel and used to estimate fetal lung maturity.

**Useful For:** Predicting fetal lung maturity and assessing the risk of developing neonatal respiratory distress syndrome, when performed during 32 to 39 weeks gestation Useful in cases in which lamellar body count results are indeterminate

**Interpretation:** Lamellar body count (LBC): Amniotic fluid LBC >50,000/mcL is predictive of fetal lung maturity. Amniotic fluid LBC <15,000/mcL is suggestive of fetal lung immaturity and increased risk of neonatal respiratory distress syndrome (RDS). The main value of fetal lung maturity testing is predicting the absence of RDS. An immature test result for fetal lung maturity is less reliable in predicting the presence of RDS.(1) Fetal Lung Profile: L/S ratio < 2.5 and PG absent: immature L/S ratio ≥ 2.5 and PG absent: indeterminate LS ratio < 2.5 and PG trace: indeterminate L/S ratio ≥ 2.5 and PG trace: mature PG present: mature

**Reference Values:**
- Immature: <15,000/mcL
- Indeterminate: 15,000-50,000/mcL
- Mature: >50,000/mcL


**Clinical References:**
algorithm (LBCR / Lamellar Body Count Reflex, Amniotic Fluid) is available to reflex indeterminate lamellar body count results for FLP / Fetal Lung Profile, Amniotic Fluid (lecithin/sphingomyelin [L/S] ratio and phosphatidylglycerol [PG] testing).

**Useful For:** Predicting fetal lung maturity and assessing the risk of developing neonatal respiratory distress syndrome, when performed during 32 to 39 weeks gestation

**Interpretation:** Amniotic fluid lamellar body count (LBC) >50,000/mcL is predictive of fetal lung maturity. Amniotic fluid LBC <15,000/mcL is suggestive of fetal lung immaturity and increased risk of neonatal respiratory distress syndrome (RDS). The main value of fetal lung maturity testing is predicting the absence of RDS. An immature test result for fetal lung maturity is less reliable in predicting the presence of RDS.(1)

**Reference Values:**
- Immature: <15,000/mcL
- Indeterminate: 15,000-50,000/mcL
- Mature: >50,000/mcL


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**Lamotrigine, Serum**

**Clinical Information:** Lamotrigine (Lamictal) is approved for therapy of bipolar I disorder and a wide variety of seizure disorders including Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and partial seizures. Its many off-label uses include treatment of migraine, trigeminal neuralgia, and treatment-refractory depression. Lamotrigine inhibits glutamate release (an excitatory amino acid) and voltage-sensitive sodium channels to stabilize neuronal membranes; it also weakly inhibits the 5-HT3 (serotonin) receptor. Lamotrigine oral bioavailability is very high (approximately 98%). The drug is metabolized by glucuronic acid conjugation to inactive metabolites. The half-life is 25 to 33 hours in adults, but decreases with concurrent use of phenytoin or carbamazepine (13-14 hours), and increases with concomitant valproic acid therapy (59-70 hours), renal dysfunction, or hepatic impairment. The therapeutic range is relatively wide, 2.5 to 15 mcg/mL for most individuals. Common adverse effects are dizziness, ataxia, blurred or double vision, nausea, or vomiting.

**Useful For:** Monitoring serum concentration of lamotrigine Assessing compliance Adjusting lamotrigine dose in patients receiving other anticonvulsant drugs which interact pharmacokinetically with lamotrigine

**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response (noncompliance?) or adverse effects, particularly when lamotrigine is co-administered with other anticonvulsant drugs. While most patients show response to the drug when the trough concentration is in the range of 2.5 to 15.0 mcg/mL, and show signs of toxicity when the peak serum concentration is >20 mcg/mL, some patients can tolerate peak concentrations as high as 70 mcg/mL.

**Reference Values:**
Patients receiving therapeutic doses usually have lamotrigine concentrations of 2.5-15.0 mcg/mL.
**Clinical References:**


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### Langust (Lobster), IgE

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### Latex, IgE

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NRHDL 29552

LDL a-High Density Cholesterol

Reference Values:

Only orderable as part of a profile. For more information see LDLD / LDL Cholesterol (Beta-Quantification), Serum.

LDLD 89652

LDL Cholesterol (Beta-Quantification), Serum

Clinical Information: Low-density lipoprotein cholesterol (LDL-C) is widely recognized as an established cardiovascular risk marker predicated on results from numerous clinical trials that demonstrate the ability of LDL-C to independently predict development and progression of coronary heart disease. In the United States, LDL-C remains the primary focus for cardiovascular risk assessment and evaluation of pharmacologic effectiveness. There have been considerable educational efforts invested and directed towards physicians, laboratorians, allied health staff, and the general public regarding LDL-C and strategies to lower LDL-C for reduction of cardiovascular risk. Low-density lipoproteins are a heterogeneous population of lipid particles classically defined as having a density of 1.006 to 1.063 kg/L.
obtained by preparative ultracentrifugation. The gold standard beta-quantification (beta-quant or BQ) method combines ultracentrifugation with precipitation and yields a collective quantitative measurement of LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and lipoprotein(a) (Lp[a]) cholesterol. In practice, LDL-C is most commonly reported using the Friedewald equation (LDL-C = TC - HDL-C - TG/5). Importantly, there are significant shortcomings and limitations to the Friedewald equation. Calculated LDL-C is not accurate in patients who are nonfasting, have triglycerides greater than 400 mg/dL, or have type III hyperlipoproteinemia. The equation is particularly inaccurate once the triglycerides are above 200 mg/dL or when LDL-C is < 70 mg/dL. Extremely low concentrations of LDL-C are associated with 2 genetic disorders; abetalipoproteinemia and hypobetalipoproteinemia. In both cases individuals will have very low total cholesterol and diminished or absent LDL-C, apolipoprotein B (apoB) (APLB / Apolipoprotein B, Plasma) and very low-density lipoprotein cholesterol (VLDL-C). Patients may exhibit clinical signs and symptoms of polyneuropathy, intestinal fat malabsorption, hepatosteatosis, and fat soluble vitamin deficiencies (VAE / Vitamin A and Vitamin E, Serum).

**Useful For:** Evaluation of cardiovascular risk Assessment of low-density lipoprotein C (LDL-C) in patients with hypertriglyceridemia, type III hyperlipoproteinemia/dysbetalipoproteinemia, or when an accurate gold standard determination of LDL-C is required Diagnosis of familial hypobetalipoproteinemia and abetalipoproteinemia

**Interpretation:** The optimal concentration for LDL cholesterol in primary prevention depends on individual patient risk. Risk factors include: family history of coronary heart disease (CHD), hypertension, cigarette smoking, obesity, diabetes mellitus, and low HDL cholesterol, among others. Consideration of drug treatment is recommended for patients with LDL cholesterol > 190 mg/dL. Values < 80 mg/dL indicate hypobetalipoproteinemia. Complications due to fat malabsorption may be present in affected individuals. Undetectable LDL-C is highly suggestive of abetalipoproteinemia. Related polyneuropathy may exist in affected individuals.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for LDL-C in adults (ages 18 years and up):
- Desirable: < 100 mg/dL
- Above Desirable: 100-129 mg/dL
- Borderline high: 130-159 mg/dL
- High: 160-189 mg/dL
- Very high: > or = 190 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for LDL-C in children and adolescents (ages 2-17 years):
- Acceptable: < 110 mg/dL
- Borderline high: 110-129 mg/dL
- High: > or = 130 mg/dL


**FLDLD**

**LDL Cholesterol, Direct**

**Interpretation:** CHD Risk Factors: +1 Age: Men, 45 years and older Women, 55 years and older or premature menopause without estrogen therapy +1 Family history of premature CHD +1 Current smoking +1 Hypertension +1 Diabetes mellitus +1 Low HDL Cholesterol: 39 mg/dL or less +1 High HDL Cholesterol: 60 mg/dL or greater LDL Cholesterol: Therapeutic goal 99 mg/dL or less if CHD is present (Optional 69 mg/dL or less) 129 mg/dL or less if no CHD and two or more risk factors 159 mg/dL or less if no CHD (Circulation 2004; 110:227-39)
Lead Profile Occupational Exposure, Blood

Clinical Information: Lead is a heavy metal commonly found in man’s environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase (ALA-D) and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Erythrocyte protoporphyrin is a biologic marker of lead toxicity. Lead inhibits several enzymes in the heme synthesis pathway and causes increased levels of RBC zinc protoporphyrin (ZPP).

Useful For: Detecting lead toxicity

Interpretation: The Centers for Disease Control and Prevention (CDC) has identified the blood lead test as the preferred test for detecting lead exposure in children. Chronic whole blood lead levels <10 mcg/dL are often seen in children. For pediatric patients, there may be an association with blood lead values of 5 to 9 mcg/dL and adverse health effects. Follow up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is >25 mcg/dL in children or >45 mcg/dL in adults. The Occupational Safety and Health Administration (OSHA) has published the following standards for employees working in industry: -Employees with whole blood lead >60 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead >50 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until whole blood lead is <40 mcg/dL. Elevated zinc protoporphyrin (ZPP) levels in adults may indicate long-term (chronic) lead exposure or may be indicative of iron deficiency anemia or anemia of chronic disease.

Reference Values:
LEAD
All ages: 0.0-4.9 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

ZINC PROTOPORPHYRIN
<100 mcg/dL


Lead with Demographics, Blood

Clinical Information: Lead is a heavy metal commonly found in man’s environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of unleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (eg, moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases.

Useful For: Detecting lead toxicity

Interpretation: The 95th percentile of the gaussian distribution of whole blood lead concentration in a population of unexposed adults is <6 mcg/dL. For pediatric patients, there may be an association with blood lead values of 5 to 9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is >25 mcg/dL in children or >45 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result >60 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels >50
mcg/dL averaged over 3 blood specimens must be removed from workplace exposure. An employee may not return to work in a lead exposure environment until their whole blood lead level is <40 mcg/dL.

**Reference Values:**

All Ages: 0.0-4.9 mcg/dL

Critical values

- Pediatrics (< or =15 years): > or =20.0 mcg/dL
- Adults (> or =16 years): > or =70.0 mcg/dL

**Clinical References:**


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**Lead, 24 Hour, Urine**

**Clinical Information:** Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before AND after chelation therapy has been used as an indicator of lead exposure. An increase in lead excretion rate in the post chelation specimen of up to 6 times the rate in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBBD / Lead with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure

**Interpretation:** Urinary excretion of <125 mcg of lead per 24 hours is not associated with any significant lead exposure. Urinary excretion >125 mcg of lead per 24 hours is usually associated with pallor, anemia, and other evidence of lead toxicity.

**Reference Values:**

0-4 mcg/specimen

Reference values apply to all ages.

**Clinical References:**


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**Lead, Hair**

**Clinical Information:** Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

**Useful For:** Detecting lead exposure

**Interpretation:** Normal hair lead content is <5.0 mcg/g. Hair lead >10.0 mcg/g indicates significant lead exposure.

**Reference Values:**

0.0-3.9 mcg/g of hair

Reference values apply to all ages.

**Clinical References:**

1. Strumylaite L, Ryselis S, Kregzdyte R: Content of lead in human hair from people exposed to lead. Int J Hyg Environ Health 2004;207:345-351
2. Barbosa F, Tanus-Santos J,

**PBNA**

**89857**

**Lead, Nails**

**Clinical Information:** Nail analysis of lead can be used to corroborate blood analysis.

**Useful For:** Detecting lead exposure

**Interpretation:** Normally, the nail lead content is <4.0 mcg/g. Nail lead >10.0 mcg/g indicates significant lead exposure.

**Reference Values:**

0.0-3.9 mcg/g of nails

Reference values apply to all ages.

**Clinical References:**
1. Strumylaite L, Ryselis S, Kregzdyte R: Content of lead in human hair from people exposed to lead. Int J Hyg Environ Health 2004;207:345-351

**PBRU**

**60246**

**Lead, Random, Urine**

**Clinical Information:** Increased urine lead concentration indicates significant lead exposure. Measurement of urine lead concentration before AND after chelation therapy has been used as an indicator of significant lead exposure. An increase in lead concentration in the postchelation specimen of up to 6 times the concentration in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBBD / Lead with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure

**Interpretation:** Urinary excretion of <4 mcg/L is not associated with any significant lead exposure. Urinary excretion >4 mcg/L is usually associated with pallor, anemia, and other evidence of lead toxicity.

**Reference Values:**

0-4 mcg/L

Reference values apply to all ages.

**Clinical References:**

**PBCRU**

**60247**

**Lead/Creatinine Ratio, Random, Urine**

**Clinical Information:** Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before AND after chelation therapy has been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the post chelation specimen of up to 6X the concentration in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional
LEFLU
60292

Leflunomide Metabolite (Teriflunomide), Serum

Clinical Information: Leflunomide is a disease-modifying antirheumatic drug approved for therapy of rheumatoid arthritis and used off-label to reduce viral nephritis in renal transplant. It is a prodrug: rapid and complete metabolism converts leflunomide to its active metabolite, teriflunomide (also called A77 1726), which acts by inhibiting pyrimidine synthesis. Teriflunomide has a very long half-life, on average >2 weeks. There is marked interindividual variability in leflunomide pharmacokinetics, thus therapeutic monitoring of serum teriflunomide concentrations may be helpful in optimizing therapy. Therapeutic targets remain only loosely defined and appear to vary depending on the purpose of therapy, but serum teriflunomide concentrations >40 mcg/mL have been associated with better clinical outcomes. Due to the long half-life, serum specimens for therapeutic monitoring may be drawn at any point in the dosing cycle, although trough (immediately before next schedule dose) sampling is preferred for consistency. Adverse reactions to leflunomide do not correlate well with serum drug concentration, but include diarrhea, hypertension, and liver toxicity. Enhanced elimination of the drug may be required in patients who are or who wish to become pregnant, or who are experiencing toxicity; teriflunomide can persist up to 2 years after ceasing therapy unless elimination is accelerated. This can be accomplished through use of activated charcoal or a bile acid sequestrant such as cholestyramine, reducing the half-life of teriflunomide to approximately 1 day. Serum concentrations <0.020 mcg/mL (<20 ng/mL) on 2 independent tests at least 2 weeks apart are preferred for patients anticipating pregnancy to minimize the potential risk of teratogenesis associated with the drug.

Useful For: Therapeutic monitoring of patients actively taking leflunomide Assessment of elimination in patients requiring enhanced elimination of the drug

Interpretation: Therapy: clinical targets for serum teriflunomide (leflunomide metabolite) concentrations are still being determined, but levels >40 mcg/mL appear to correlate with better outcome. Elimination: serum concentrations <0.020 mcg/mL (20 ng/mL) are preferred to minimize potential teratogenesis for patients considering pregnancy.

Reference Values:
Therapeutic: >40 mcg/mL
Elimination: <0.020 mcg/mL

**Legionella Antigen, Urine**

**Clinical Information:** Legionnaire's disease, named after the outbreak in 1976 at the American Legion convention in Philadelphia, is caused by Legionella pneumophila and is an acute febrile respiratory illness ranging in severity from mild illness to fatal pneumonia. Since that time, it has been recognized that the disease occurs in both epidemic and endemic forms, and that sporadic cases are not readily differentiated from other respiratory infections by clinical symptoms. It is estimated that about 25,000 to 100,000 Legionella infections occur annually. Known risk factors include: immunosuppression, cigarette smoking, alcohol consumption, and concomitant pulmonary disease. The resulting mortality rate, which ranges up to 40% in untreated immunocompetent patients, can be lowered if the disease can be rapidly diagnosed and appropriate antimicrobial therapy instituted early. Legionella pneumophila is estimated to be responsible for 80% to 85% of reported cases of Legionella infections with the majority of cases being caused by Legionella pneumophila serogroup 1 alone. A variety of laboratory techniques (culture, direct fluorescent antibody, DNA probes, immunoassay, antigen detection), using a variety of specimen types (respiratory specimens, serum, urine), have been used to help diagnose Legionella pneumonia. Respiratory specimens are preferred. Unfortunately, one of the presenting signs of Legionnaires disease is the relative lack of productive sputum. This necessitates the use of invasive procedures to obtain adequate specimens (eg, bronchial washing, transtracheal aspirate, lung biopsy) in many patients. Serology may also be used, but is often retrospective in nature. It was shown as early as 1979 that a specific soluble antigen was present in the urine of patients with Legionnaires disease. (1) The presence of Legionella antigen in urine makes this an ideal specimen for collection, transport, and subsequent detection in early, as well as later, stages of the disease. The antigen may be detectable in the urine as early as 3 days after onset of symptoms.

**Useful For:** As an adjunct to culture for the presumptive diagnosis of past or current Legionnaires disease (Legionella pneumophila serogroup 1)

**Interpretation:** Positive Presumptive positive for Legionella pneumophila serogroup 1 antigen in urine, suggesting current or past infection. Culture is recommended to confirm infection. Negative Presumptive negative for Legionella pneumophila serogroup 1 antigen in urine, suggesting no recent or current infection. Infection with Legionella cannot be ruled out because: - Other serogroups (other than serogroup 1, which is detected by this assay) and other Legionella species (other than Legionella pneumophila) can cause disease - Antigen may not be present in urine in early infection - The level of antigen may be below the detection limit of the test Legionella culture is recommended for cases of suspected Legionella pneumonia due to organisms other than Legionella pneumophila serogroup 1.

**Reference Values:**
Negative (reported as positive or negative)

**Clinical References:**

---

**Legionella Culture**

**Clinical Information:** The Legionellaceae are ubiquitous in natural fresh water habitats, allowing them to colonize man-made water supplies, which may then serve as the source for human infections. Legionella pneumophila and the related species, Legionella bozemanii, Legionella dumoffii, Legionella gormanii, Legionella micdadei, Legionella longbeachae, and Legionella jordanis have been isolated from patients with pneumonia (Legionnaires disease). The organism has been isolated from lung tissue, bronchoalveolar lavage, pleural fluid, transtracheal aspirates, and sputum. The signs, symptoms, and radiographic findings of Legionnaires disease are generally nonspecific.
Useful For: Diagnosis of Legionnaires disease Because examination by rapid PCR increases sensitivity and provides faster results, Mayo Medical Laboratories strongly recommends also ordering LEGRP / Legionella species, Molecular Detection, PCR.

Interpretation: Identification of Legionella species from respiratory specimens provides a definitive diagnosis of Legionnaires disease. Organisms isolated are identified as Legionella species via MALDI-TOF MS and/or 16S rRNA gene sequencing.

Reference Values:
No growth

Identification of Legionella species.


Legionella pneumophila (Legionnaires Disease), Antibody, Serum

Clinical Information: Legionella pneumophila may cause pulmonary disease in both normal and immunocompetent hosts. The disease may occur sporadically in the form of community acquired pneumonia and in epidemics. Pneumonia (often referred to as Legionnaires disease) occurs more frequently in severely immunosuppressed individuals; a milder form of the illness, referred to as Pontiac fever, is more prevalent in normal hosts. Extrapulmonary infection with Legionella pneumophila is rare. Legionnaire's disease, Pontiac fever, and extrapulmonary infection have been collectively referred to as legionellosis. Approximately 85% of the documented cases of legionellosis have been caused by Legionella pneumophila. Serogroups 1 and 6 of Legionella pneumophila, by themselves, account for up to 75% of cases of legionellosis. The definitive diagnosis of Legionella pneumophila is made by isolation of the organism on specialized culture medium (buffered charcoal yeast extract agar). Pulmonary secretions can be directly examined using a direct fluorescent antibody procedure, but the sensitivity of this method is low (25%-70%). Often it is difficult for the patient to produce pulmonary secretion (sputum) for examination, the pneumonia is frequently interstitial and sputum is scant. In the absence of invasive procedures (eg, bronchial alveolar lavage), urine evaluation for Legionella pneumophila antigen or indirect serological (antibody) methods may be useful.

Useful For: Evaluation of possible legionellosis (Legionnaires disease, Pontiac fever, extrapulmonary legionella infection caused by Legionella pneumophila)

Interpretation: A negative result indicates that IgG/A/M antibody to Legionella pneumophila serogroups 1-6 is not detected. Negative results do not exclude Legionella infection. It may require 4 to 8 weeks to develop a detectable antibody response; serum specimens taken early in the course of infection may not yet have significant antibody titers. Furthermore, antibody levels can fall to undetectable levels within a month of infection, early antibiotic therapy may suppress antibody response, and some individuals may not develop antibodies above detectable limits. Some culture-positive cases of Legionella do not develop Legionella antibody. Positive results are suggestive of Legionella infection; however, a single positive result only indicates immunologic exposure at some time. It does not distinguish between previous or current infection. The level of antibody response may not be used to determine active infection. Other laboratory procedures or additional clinical information are necessary to establish a diagnosis. Specimens with equivocal results are retested prior to reporting. Repeat testing on a second specimen should be considered in patients with equivocal results, if clinically indicated.

Reference Values:
Negative

Legionella pneumophila Antibodies (IgM)

**Reference Values:**
Reference Range: <1:16

IgM antibodies to Legionella pneumophila serogroup 1 and 6 additional L. pneumophila serogroups (2,3,4,5,6,8) are measured using an IgM specific conjugate. We recommend that the IgM test always be performed in conjunction with the polyvalent antibody test.

The IgM response to Legionella tends to develop concurrently with the IgG response and may remain elevated as long as the IgG response remains elevated. Cross-reactions have been described with several species of bacteria and mycoplasma.

**Legionella species, Molecular Detection, PCR**

**Clinical Information:** Legionnaires disease was first recognized during a pneumonia outbreak at the Legionnaires convention in Philadelphia in 1976. Investigators with the CDC isolated a novel, gram-negative bacillus, later named Legionella pneumophila. It is now widely recognized that Legionella pneumophila (and other members of the genus Legionella) cause Legionnaires disease.

**Useful For:** Sensitive and rapid diagnosis of pneumonia caused by Legionella species

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Legionella 5S rRNA gene indicates the presence of a Legionella species DNA, which may be due to Legionella infection or environmental/water Legionella DNA in the specimen. A negative PCR result indicates the absence of detectable Legionella DNA in the specimen, but does not rule-out legionellosis as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Legionella species in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**Leishmaniasis (Visceral) Antibody, Serum**

**Clinical Information:** Visceral leishmaniasis (kala azar) is a disseminated intracellular protozoal infection that targets primarily the reticuloendothelial system (liver, spleen, bone marrow) and is caused by Leishmania donovani, Leishmania chagasi, or Leishmania infantum (Leishmania donovani complex). Transmission is by the bite of sandflies. Clinical symptoms include fever, weight loss, and splenomegaly; pancytopenia and hypergammaglobulinemia are often present. Most (90%) new cases each year arise in rural areas of India, Nepal, Bangladesh, Sudan, and Brazil but the disease has a worldwide distribution, including the Middle East. Definitive diagnosis has required the microscopic documentation of characteristic intracellular amastigotes in stained smears from culture of aspirates of tissue (spleen, lymph node) or bone marrow. The detection of serum antibodies to the recombinant K39 antigen of Leishmania donovani is an alternative noninvasive sensitive (95%-100%) method for the diagnosis of active, visceral leishmaniasis.
**Useful For:** Diagnosis of active visceral leishmaniasis

**Interpretation:** A positive result is consistent with a diagnosis of active visceral leishmaniasis.

**Reference Values:**
- Negative

**Clinical References:**

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**Lemon IgG**

**Interpretation:** mcg/mL of IgG
- Lower Limit of Quantitation: 2.0
- Upper Limit of Quantitation: 200

**Reference Values:**
- <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Lemon, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
- Class IgE kU/L Interpretation
  - 0: Negative
  - 1: 0.35-0.69: Equivocal

Lentil IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Lentil, IgE

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
</tbody>
</table>
LEPD
82849

Lepidoglyphus destructor, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**FLEP 91339**  
**Leptin**  
**Reference Values:**  
Units: ng/mL  

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (BMI=22)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.7 - 5.3</td>
</tr>
<tr>
<td>Females</td>
<td>3.3 - 18.3</td>
</tr>
</tbody>
</table>

Contact laboratory for other BMI reference ranges.

Test Performed By: Esoterix Endocrinology  
4301 Lost Hills Road  
Calabasas Hills, CA 91301

**FLEPM 75098**  
**Leptospira Antibody, IgM by Dot Blot**  
**Interpretation:** Samples interpreted as negative indicate that antibody is not present in the sample, or is below the detection level of the method. Since antibodies may not be present during early disease, confirmation two to three weeks later is recommended. An initially-negative result followed by a positive result indicates IgM seroconversion. Equivocal specimens should be cautiously interpreted. Further testing with an additional specimen is recommended. If the specimen remains equivocal, a second serological method should be considered if leptospirosis infection is still suspected. Samples interpreted as positive may indicate the specific antibody. Antibody presence alone cannot be used for diagnosis of acute infection, however, because antibodies from prior exposure may circulate for a prolonged period of time.

**Reference Values:**  
Negative: No significant level of Leptospira IgM antibody detected.  
Equivocal: Questionable presence of Leptospira IgM antibody detected. Repeat testing in 10-14 days may be helpful.  
Positive: Presence of IgM antibody to Leptospira detected, suggestive of a current or recent infection.

**FLETG 57639**  
**Lettuce IgG**  
**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation: 2.0  
Upper Limit of Quantitation: 200

**Reference Values:**  
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**LETT 82805**  
**Lettuce, IgE**  
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

**Interpretation:** Report will include a summary of the procedure.

**Reference Values:**
Not applicable

**Clinical References:**

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**Leukemia/Lymphoma Immunophenotyping by Flow Cytometry**

**Clinical Information:** Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features. This test is appropriate for hematopoietic specimens only. If your specimen is a solid tissue, order LLPT / Leukemia/Lymphoma Immunophenotyping by Flow Cytometry, Tissue.

**Useful For:** Evaluating lymphocytes of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subclassification of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasias from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

**Interpretation:** Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

**Reference Values:**
An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

**Clinical References:** 1. Hanson CA, Kurtin PJ, Katzman JA, et al: Immunophenotypic analysis of

**Leukemia/Lymphoma Immunophenotyping by Flow Cytometry, Tissue**

**Clinical Information:** Cellular immunophenotyping, characterizing cells by using antibodies directed against cell surface markers, is generally regarded as a fundamental element in establishing a diagnosis of tissue involvement by hematolymphoid malignancies, when used in conjunction with morphologic assessment. It is also an essential component in subclassification of hematolymphoid malignancies, when present.

**Useful For:** Evaluation of tissues for potential involvement by: -Chronic lymphoproliferative disorders -Malignant lymphomas -Acute lymphoblastic leukemia -Acute myelogenous leukemia

**Interpretation:** Normal tissues typically contain a mixture of B cells with polytypic surface immunoglobulin light chain expression and T cells with unremarkable expression of the T cell-associated antigens CD3, CD5, and CD7. Typically, no appreciable blast population is present by CD45 and side scatter analysis.

**Reference Values:** An interpretive report will be provided.


**Leukocyte Adhesion Deficiency Type 1, CD11a/CD18 and CD11b/CD18 Complex Immunophenotyping, Blood**

**Clinical Information:** Leukocyte adhesion deficiency syndrome type 1 (LAD-1) is an autosomal recessive disorder caused by mutations in the common chain (CD18) of the beta2-integrin family. LAD-1 is clinically characterized by recurrent infections, impaired wound healing, delayed umbilical cord separation, persistent leukocytosis, and recurrent soft tissue and oral infections. Each of the beta2-integrins is a heterodimer composed of an alpha chain (CD11a, CD11b, or CD11c) noncovalently...
linked to a common beta2-subunit (CD18). The alpha-beta heterodimers of the beta2-integrin family include LFA-1 (CD11a/CD18), Mac-1/CR3 (CD11b/CD18), and p150/95 (CD11c/CD18). The CD18 gene, ITGB2, and its product are required for normal expression of the alpha-beta heterodimers. Therefore, defects in CD18 expression lead to either very low or no surface membrane expression of CD11a, CD11b, and CD11c. Severe and moderate forms of LAD-1 exist, differing in the degrees of protein deficiency, which are caused by different ITGB2 mutations. Two relatively distinct clinical phenotypes of LAD-1 have been described. Patients with the severe phenotype (<1% of normal expression of CD18 on neutrophils) characteristically have delayed umbilical stump separation (>30 days), infection of the umbilical stump (omphalitis), persistent leukocytosis (>15,000/microliter) in the absence of overt active infection, and severe destructive gingivitis with periodontitis and associated tooth loss, and alveolar bone resorption. Patients with the moderate phenotype of LAD-1 (1%-30% of normal expression of CD18 on neutrophils) tend to be diagnosed later in life. Normal umbilical separation, lower risk of life-threatening infections, and longer life expectancy are common in these patients. However, leukocytosis, periodontal disease, and delayed wound healing are still very significant clinical features. Patients with LAD-1 (and other primary immunodeficiency diseases) are unlikely to remain undiagnosed in adulthood. Consequently, this test should not be typically ordered in adults for LAD-1. However, it may be also used to assess immune competence by determining CD18, 11a, and 11b expression.

**Useful For:** As an aid in the diagnosis of LAD-1 syndrome, primarily in patients <18 years of age CD11a, CD11b, and CD18 phenotyping

**Interpretation:** The report will include a summary interpretation of the presence or reduction in the level of expression of the individual markers (CD11a, CD11b, and CD18). Expression of the individual markers provides indirect information on the presence or absence of the CD11a/CD18 and CD11b/CD18 complexes. Specimens obtained from patients with LAD-1 show significant reduction (moderate phenotype) or near absence (severe phenotype) of CD18 and its associated molecules, CD11a and CD11b, on neutrophils and other leukocytes. CD11c expression also is low in LAD-1. The analytical sensitivity of the CD11c assay is insufficient to allow interpretation of CD11c surface expression. Therefore, we test only for expression of CD18, CD11a, and CD11b.

**Reference Values:**
Normal (reported as normal or absent expression for each marker)

**Clinical References:**

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**Leukotriene E4, Urine**

**Clinical Information:** Leukotrienes (LTs) are eicosanoids generated from arachidonic acid via the 5-lipoxygenase pathway. Leukotriene E4 (LTE4) is the stable end product of this pathway and therefore regarded as a biomarker of total cysteinyl leukotriene (cys-LT) production. Assessment of LTE4 in urine allows for noninvasive specimen collection and avoids artifactual formation of LTs during phlebotomy. Generation of LTE4 occurs nonspecifically from active mast cells, basophils, eosinophils, and macrophages, and modulated through a variety of mechanisms. Elevated concentrations of LTE4 are associated with inflammatory and accelerated mast cell activation conditions, specifically in patients with systemic mast cell disease. Systemic mastocytosis (SM), or systemic mast cell disease, is a myeloproliferative neoplasm which has infiltrated extracutaneous organs. Release of mast cell inflammatory mediators leads to disease symptoms including those associated with allergic and anaphylactic reactions, while increased mast cell number leads to organ dysfunction. Consensus diagnostic criteria for SM include 1 major criterion: imaging of the multifocal infiltrates; and 4 minor
criteria: 1) identifying morphological features of >25% of mast cells from bone marrow biopsy, 2) detection of the point mutation at codon 816 in the KIT gene, 3) CD2 and/or CD25 expression in mast cells, and 4) persistently elevated serum tryptase. Diagnosis requires either 1 major plus 1 minor criterion or 3 minor criteria. (2) Measurement of urinary mast cell activation biomarkers can aid in the initial evaluation of suspected cases of systemic mast cell disease, potentially avoiding the need for imaging and bone marrow examination. Patients with SM frequently have elevated urine concentrations of LTE4(1), N-methylhistamine(3,4), and/or 2,3-dinor 11 beta-prostaglandin F2 alpha. (4) Urinary LTE4 has also demonstrated significant utility in patients with asthma and respiratory diseases. In a study of adults with mild to moderate asthma on 5-lipoxygenase inhibitors, urine LTE4 concentrations decreased approximately 40% compared to asthma control subjects, suggesting modest decreases in LTE4 production correlates with clinical improvements in asthma severity.

**Useful For:** An aid to evaluate patients suspected of having systemic mastocytosis

**Interpretation:** Elevated urinary leukotriene E4 (LTE4) concentrations >104 pg/mg creatinine are consistent with the diagnosis of systemic mast cell disease when combined with clinical signs and symptoms. Pharmacological treatment with 5-lipoxygenase inhibitors or leukotriene receptor antagonists has been shown to decrease production of LTE4. Urinary LTE4 may be used together with serum tryptase, urinary 2,3-dinor 11 beta-prostaglandin F2 alpha, and/or urinary N-methyl histamine.

**Reference Values:**

< or =104 pg/mg creatinine

**Clinical References:**


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**Levetiracetam, Serum**

**Clinical Information:** Levetiracetam is approved for treatment of partial, myoclonic, and tonic-clonic seizures, and is used off-label for manic states and migraine prophylaxis. Levetiracetam has very favorable pharmacokinetics with good bioavailability and rapid achievement of steady state. Its hepatic metabolism is minimal and nonoxidative, making it safe for use with hepatic enzyme inducers or inhibitors. The major metabolite is a carboxylic acid derivate, which is inactive and accounts for roughly one quarter of the administered dose. Levetiracetam is excreted renally, with a mean half-life of 7 hours in adults and slightly less than that in children. Renal dysfunction may warrant therapeutic monitoring and/or dose adjustment. Given the lack of drug interactions and favorably pharmacokinetics, the primary uses for therapeutic drug monitoring of levetiracetam are compliance assurance and management of physiological changes such as puberty, pregnancy, and aging. Toxicities associated with levetiracetam use include decreased hematocrit and red blood cell count, decreased neutrophil count, somnolence, asthenia, and dizziness. These toxicities may be associated with blood concentrations in the therapeutic range.

**Useful For:** Monitoring serum concentration of levetiracetam, particularly in patients with renal disease Assessing compliance Assessing potential toxicity

**Interpretation:** Most individuals display optimal response to levetiracetam with serum levels 12 to 46 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Toxic levels have not been well established. Therapeutic ranges are based on specimen drawn at trough (ie, immediately before the next dose).

**Reference Values:**

12.0-46.0 mcg/mL

**FLEVO**

**Levodopa, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis
Steady state during chronic 3 to 8 gram p.o. dose: 0.2-3 mcg/mL plasma.

**LIDO**

**Lidocaine, Serum**

**Clinical Information:** Lidocaine is commonly used as a local anesthetic, but is also effective at controlling ventricular arrhythmia and ventricular fibrillation in children and adults. For cardiac therapy, optimal therapeutic response is seen when serum concentrations are between 1.5 and 5.0 mcg/mL. Lidocaine is 50% protein-bound, primarily to alpha-1-acid glycoprotein; concentrations of this protein increase after myocardial infarction, which may decrease the amount of free lidocaine and thus its efficacy. Lidocaine undergoes extensive first-pass hepatic metabolism and, thus, is not administered orally. It is eliminated via renal clearance, with a half-life of approximately 1.5 hours. Diseases that reduce hepatic or renal function reduce clearance and prolong elimination of lidocaine. Toxicity occurs when the concentration of lidocaine is >6.0 mcg/mL and is usually associated with symptoms of central nervous system excitation, light-headedness, confusion, dizziness, tinnitus, and blurred or double vision. This can be accompanied by bradycardia and hypotension leading to cardiovascular collapse.

**Useful For:** Assessing optimal dosing during the acute management of ventricular arrhythmias following myocardial infarction or during cardiac manipulation such as surgery Assessing potential toxicity

**Interpretation:** Optimal response to lidocaine occurs when the serum concentration is between 1.5 and 5.0 mcg/mL. Toxicity is more likely when concentrations exceed 6.0 mcg/mL.

**Reference Values:**
Therapeutic: 1.5-5.0 mcg/mL
Critical value: >6.0 mcg/mL

3. Harrison DC: Should lidocaine be administered routinely to all patients after acute myocardial infarction? Circulation 1978;58:581-584

**LIME**

**Lime, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Limulus Amebocyte Lysate (Endotoxin)**

**FLALA 57193**

**Reference Values:**

<table>
<thead>
<tr>
<th>LEVEL DETECTED</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.05 EU/mL</td>
<td>None Detected</td>
</tr>
<tr>
<td>0.125 EU/mL</td>
<td>Action level for dialysis water</td>
</tr>
<tr>
<td>&lt;0.25 EU/mL</td>
<td>Maximum allowable level for dialysis water and USP acceptable limits for injectable or irrigation water</td>
</tr>
<tr>
<td>0.25 EU/mL</td>
<td>Action level for dialysis fluid</td>
</tr>
<tr>
<td>&lt;0.50 EU/mL</td>
<td>Maximum allowable level for dialysis fluid and USP acceptable limits for inhalatory water.</td>
</tr>
<tr>
<td>2.00 EU/mL</td>
<td>Acceptable upper limit for Hemodialysis reuse water.</td>
</tr>
</tbody>
</table>

The LAL is used as a quantitative test to detect gram-negative endotoxin in aqueous solutions used in patient management. The LAL assay is not recommended for serum or plasma samples due to the presence of inhibitory factors. It is essential to maintain specimen sterility and prevent false positive results from exogenous gram negative bacteria.

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**Linden, IgE**

**LIND 82862**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing are chosen...
often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Linseed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or ≥100 Strongly positive Reference values apply to all ages.

Clinical References: Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders

LPSBF 83690 Lipase, Body Fluid
Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids
and produce fatty acids and 1-acylglycerol. Bile salts and a cofactor, colipase, are required for full
catalytic activity and greatest specificity. The pancreas is the primary source of serum lipase. Both lipase
and colipase are synthesized in the pancreatic acinar cells and secreted by the pancreas in roughly
equimolar amounts. Serum lipase is filtered and reabsorbed by the kidneys. Pancreatic injury results in
increased serum lipase levels. In pancreatitis, serum lipase becomes elevated at about the same time as
serum amylase (in 4-8 hours). But serum lipase may rise to a greater extent and remain elevated much
longer (7-10 days) than serum amylase. Elevations in serum lipase up to 50 times the upper reference
values have been reported. The increase in serum lipase is not necessarily proportional to the severity of
the attack and normalization is not necessarily a sign of resolution. Both lipase and amylase should be
very elevated in peritoneal fluid arising from the pancreas. Values in fluid of pancreatic origin should be
at least several-fold higher than serum drawn at the same time, even in acute pancreatitis.

Useful For: Investigating pancreatic disorders, usually pancreatitis or pancreatic pseudocysts

Interpretation: Very high values are consistent with pancreatic pseudocysts.

Reference Values: Not applicable

FLIPR 90347 Lipase, Random Urine
Reference Values:
Adult: 4 U/L or less

LPS 8328 Lipase, Serum
Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids
and produce fatty acids and 2-acylglycerol. Bile salts and a cofactor, colipase, are required for full
catalytic activity and greatest specificity. The pancreas is the primary source of serum lipase. Both lipase
and colipase are synthesized in the pancreatic acinar cells and secreted by the pancreas in roughly equimolar amounts. Lipase is filtered and reabsorbed by the kidneys. Pancreatic injury results in increased serum lipase levels.

**Useful For:** Investigating pancreatic disorders, usually pancreatitis

**Interpretation:** In pancreatitis, lipase becomes elevated at about the same time as amylase (in 4-8 hours). But lipase may rise to a greater extent and remain elevated much longer (7-10 days) than amylase. Elevations 2 to 50 times the upper reference have been reported. The increase in serum lipase is not necessarily proportional to the severity of the attack. Normalization is not necessarily a sign of resolution. In acute pancreatitis, normoamylasemia may occur in up to 20% of such patients. Likewise, the existence of hyperlipemia may cause a spurious normoamylasemia. For these reasons, it is suggested that the 2 assays complement and not exclude each other, and that both enzymes should be assayed.

**Reference Values:**

> or =16 years: 10-73 U/L

Reference values have not been established for patients that are <16 years of age.

**Clinical References:**


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**Lipid Analysis, Body Fluid**

**Clinical Information:** The presence of a chylous effusion, which results from lymphatic drainage into a body cavity, can be determined by identifying triglycerides and chylomicrons in the fluid. Catheter-related iatrogenic effusions can be identified by determining the presence of intravenous solution constituents in the fluid.

**Useful For:** Distinguishing between chylous and nonchylous effusions Identifying iatrogenic effusions

**Interpretation:** Triglyceride concentration >110 mg/dL is highly suggestive of a chylous effusion.

**Reference Values:**

Not applicable

**Clinical References:**


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**Lipid Panel**

**Clinical Information:** Cardiovascular disease is the number 1 cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually, many in individuals who have no prior symptoms. Prevention of ischemic cardiovascular events is key. Risk factors, including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, are used by physicians to identify individuals likely to have an ischemic event.

**Useful For:** Evaluation of cardiovascular risk

**Interpretation:** Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Medical Laboratories reports (see Reference Values).

**Reference Values:**

The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non HDL cholesterol) in adults ages 18 and up:
TOTAL CHOLESTEROL
Desirable: <200 mg/dL
Borderline high: 200-239 mg/dL
High: > or =240 mg/dL

TRIGLYCERIDES
Normal: <150 mg/dL
Borderline high: 150-199 mg/dL
High: 200-499 mg/dL
Very high: > or =500 mg/dL

HDL CHOLESTEROL
Males
> or =40 mg/dL
Females
> or =50 mg/dL

LDL CHOLESTEROL
Desirable: <100 mg/dL
Above Desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

NON HDL CHOLESTEROL
Desirable: <130 mg/dL
Above Desirable: 130-159 mg/dL
Borderline High: 160-189 mg/dL
High: 190-219
Very high: > or =220 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17:

TOTAL CHOLESTEROL
Acceptable: <170 mg/dL
Borderline high: 170-199 mg/dL
High: > or =200 mg/dL

TRIGLYCERIDES
2-9 years:
Acceptable: <75 mg/dL
Borderline high: 75-99 mg/dL
High: > or =100 mg/dL
10-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL

HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline low: 40-45 mg/dL
Acceptable: >45 mg/dL

LDL CHOLESTEROL
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL
Lipoprotein (a) Cholesterol, Serum

Clinical Information: Lipoprotein(a) (Lp[a]) is a highly heterogeneous molecule, consisting of a low-density lipoprotein (LDL) with a highly glycosylated apolipoprotein(a) (apo[a]) covalently linked to the apolipoprotein B moiety of LDL via a single disulfate bond. Lp(a) has been associated with atherogenesis and promotion of thrombosis. Increased levels of Lp(a) have been estimated to confer a 1.5 to 3.0-fold increased risk for coronary artery disease (CAD) in many but not all studies. Apo(a) has approximately 80% structural homology with plasminogen, but does not contain the active site for fibrin cleavage. One proposed mechanism for Lp(a)'s atherogenicity is competition for binding sites with plasminogen during fibrin clot formation and the resulting inhibition of fibrinolysis. Recently a high correlation was demonstrated between Lp(a) and oxidized LDL, suggesting that the atherogenicity of Lp(a) lipoprotein may be mediated in part by associated proinflammatory oxidized phospholipids. The heterogeneity of Lp(a) arises mainly from the variable number of kringle repeats in the apo(a) portion of the molecule. Kringles are specific structural domains containing 3 intra-strand disulfide bonds that are highly homologous to similar repeats found in plasminogen. In the clinical laboratory, immunologic methods are generally used to quantify Lp(a) protein mass. Reagents for Lp(a) mass measurement are available from multiple manufacturers and although standardization efforts are underway, currently available methods are not standardized. Difficulties in standardizing Lp(a) mass measurement arise from the variability in signals produced by different reagents due to the size polymorphisms of apo(a). For this reason, some elevations of Lp(a) mass are associated with low levels of Lp(a) cholesterol. Lp(a) quantification can be done by densitometric measurement of Lp(a) cholesterol. This method measures only the cholesterol contained in the Lp(a) particles and is thus not influenced by the relative size of the apo(a) particle. Because Lp(a) cholesterol measurement is not influenced by apo(a) size, it may provide a more specific assessment of cardiovascular risk than Lp(a) mass measurement. Lp(a) cholesterol measurement may be used in concert with Lp(a) mass determination, or may be used as a stand-alone test for assessment of risk.

Useful For: Evaluation of increased risk for cardiovascular disease and events: -Most appropriately measured in individuals at intermediate risk for cardiovascular disease -Patients with early atherosclerosis or strong family history of early atherosclerosis without explanation by traditional risk factors should also be considered for testing Follow-up evaluation of patients with measurable lipoprotein(a) protein (LIPA)

Interpretation: Patients with increased Lp(a) cholesterol values have an approximate 2-fold increased risk for developing cardiovascular disease and events. Lipoprotein-X (LpX) is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice, and is an indicator of cholestasis. The presence of LpX will be reported if noted during Lp(a) cholesterol analysis.

Reference Values:
Lp(a) CHOLESTEROL
Normal: <3 mg/dL
Suggests increased risk of coronary artery disease: > or =3 mg/dL

LpX
Undetectable

Lipoprotein (a), Serum

Clinical Information: Lipoprotein (a) (Lp[a]) consists of an LDL particle that is covalently bound to an additional protein, apolipoprotein (a) (Apo[a]). Apo(a) has high-sequence homology with the coagulation factor plasminogen and, like LDL, Lp(a) contains apolipoprotein B100 (ApoB). Thus, Lp(a) is both proatherogenic and prothrombotic. Lp(a) is an independent risk factor for coronary heart disease (CHD), ischemic stroke, and aortic valve stenosis. Lp(a) has been referred to as "the most atherogenic lipoprotein." The mechanism of increased risk is unclear but most likely involves progression of atherosclerotic stenosis via intimal deposition of cholesterol and promotion of thrombosis via homology to plasminogen. Concentrations of Lp(a) particles in the blood can be expressed readily by 2 methods: as concentrations of Lp(a) protein or as Lp(a) cholesterol. Mayo's Cardiovascular Laboratory Medicine measures and reports Lp(a) cholesterol individually (LPAWS / Lipoprotein [a] Cholesterol, Serum) and as a part of the lipoprotein profile (LMPP / Lipoprotein Metabolism Profile). The cholesterol content of Lp(a) particles varies little, and Lp(a) can contain significant proportions of the serum cholesterol. Unlike Lp(a) cholesterol, accurate immunochemical measurement of Lp(a)-specific protein, is complicated by the heterogeneity of Lp(a) molecular size. Due to the large number of polymorphisms in the population any given individual can have an Apo(a) protein between 240 to 800 kDa. This heterogeneity leads to inaccuracies when results are expressed in terms of mg/dL of protein. In addition, the degree of atherogenicity of the Lp(a) particle may depend on the molecular size of the Lp(a)-specific protein. Serum concentrations of Lp(a) are related to genetic factors, and are largely unaffected by diet, exercise and lipid-lowering pharmaceuticals. However, in a patient with additional modifiable CHD risk factors, more aggressive therapy to normalize these factors may be indicated if the Lp(a) value is also increased.

Useful For: Cardiovascular disease (CVD) risk refinement in patients with moderate or high risk based on conventional risk factors

Interpretation: The frequency distribution of serum lipoprotein (a) (Lp[a]) concentrations is markedly skewed toward the low end, with approximately 85% of the population having concentrations <30 mg/dL. Lp(a) concentrations >30 mg/dL are associated with 2- to 3-fold increased risk of cardiovascular events independent of conventional risk markers.

Reference Values:
< or =30 mg/dL
Values >30 mg/dL may suggest increased risk of coronary heart disease.

Clinical Information: Lipoprotein metabolism profile analysis adds practical information about the etiology of cholesterol and/or triglyceride elevation. In some patients, increased serum lipids reflects elevated levels of intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), lipoprotein a (Lp[a]), or even the abnormal lipoprotein complex-LpX. These elevations can be indicative of a genetic deficiency in lipid metabolism or transport, nephrotic syndrome, endocrine dysfunction or even cholestasis. Identification of the lipoprotein associated with lipid elevation is achieved using the gold-standard methods, which include ultracentrifugation, selective precipitation, electrophoresis, and direct measurement of cholesterol and triglycerides in isolated lipoprotein fractions. Proper characterization of a patient’s dyslipidemic phenotype aids clinical decisions and guides appropriate therapy. Classifying the hyperlipoproteinemias into phenotypes places disorders that affect plasma lipid and lipoprotein concentrations into convenient groups for evaluation and treatment. A clear distinction must be made between primary (inherited) and secondary (liver disease, alcoholism, metabolic diseases) causes of dyslipoproteinemia. Lipoprotein profiling will identify the presence of Lp(a) and LpX and distinguish between the following dyslipemias: -Exogenous hyperlipemia (Type I) -Familial Hypercholesterolemia (Type IIa) -Familial Combined Hyperlipidemia (Type IIb) -Familial dysbetalipoproteinemia (Type III) -Endogenous hyperlipemia (Type IV) -Mixed hyperlipemia (Type V)

Useful For: Diagnosing dyslipoproteinemia Quantitation of cholesterol and triglycerides in very-low-density lipoprotein (VLDL), LDL, HDL, and chylomicrons Identification of LpX Classifying hyperlipoproteinemias (lipoprotein phenotyping) Evaluating patients with abnormal lipid values (cholesterol, triglyceride, HDL, LDL) Quantifying lipoprotein a (Lp[a]) cholesterol

Interpretation: For discussion of primary disorders associated with dyslipemias see Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions. For discussion of Lp(a), see LPAWS / Lipoprotein (a) Cholesterol, Serum.

Reference Values:

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-9 years</td>
<td>10-17 years</td>
<td>&gt;18 years</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>** Acceptable: high: 170-199 High: &gt; or =200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>** Acceptable: high: 75-99 High: &gt; or =100</td>
<td>** Acceptable: high: 90-129 High: &gt; or =130</td>
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<td></td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td>** Acceptable: high: 110-129 High: &gt; or =130</td>
<td></td>
<td></td>
<td>*** Desirable: Desirable: 100-129 Borderline high: 130-159 High: 160-189 Very high: &gt; or =190</td>
</tr>
<tr>
<td>LDL Triglycerides (mg/dL)</td>
<td>&lt; or = 50</td>
<td></td>
<td></td>
<td>&lt; or = 50</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>** Acceptable: high: 90-109 High: &gt; or =110</td>
<td></td>
<td></td>
<td>Desirable: Desirable: 90-99 Borderline high: 100-119 High: 120-139 Very high: &gt; or =140</td>
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<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>** Low: low: 40-45 Acceptable: &gt; 45</td>
<td></td>
<td></td>
<td>*** Males: &gt; or =40 Females: &gt; or =50</td>
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<tr>
<td>VLDL Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL Triglycerides (mg/dL)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Beta VLDL Cholesterol (mg/dL)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Beta VLDL Triglycerides (mg/dL)</td>
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<tr>
<td>Chylomicron Cholesterol</td>
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<td></td>
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<tr>
<td>Chylomicron Triglycerides</td>
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<td>Undetectable</td>
</tr>
<tr>
<td>Lp(a) cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Lithium, Serum**

**Clinical Information:** Lithium alters the intraneuronal metabolism of catecholamines by an unknown mechanism. It is used to suppress the manic phase of manic-depressive psychosis. Lithium is distributed throughout the total water spaces of the body and is excreted primarily by the kidney. Toxicity from lithium salts leads to ataxia, slurred speech, and confusion. Since the concentration of lithium in the serum varies with the time after the dose, blood for lithium determination should be drawn at a standard time, preferably 8 to 12 hours after the last dose (trough values).

**Useful For:** Monitoring therapy of patients with bipolar disorders, including recurrent episodes of mania and depression Evaluating toxicity

**Interpretation:** The therapeutic range for lithium has been established at 0.5 to 1.2 mmol/L. Within this range, most people will respond to the drug without symptoms of toxicity. However, response and side effects will be individual. Lithium concentrations and side effects can also increase with the loss of salt and water from the body, which can occur with a salt-free diet, excessive sweating, or an illness that causes vomiting and diarrhea. A variety of prescribed drugs, over-the-counter medications, and supplements can also increase, decrease, or interfere with the concentrations of lithium.

**Reference Values:**
- Therapeutic: 0.5-1.2 mmol/L (trough concentration)
- Critical value: >1.6 mmol/L

There is no relationship between peak concentration and degree of intoxication.

**Clinical References:**
### Liver Fibrosis, Fibro Test-ActiTest Panel

#### Reference Values:

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
</tr>
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</tr>
<tr>
<td>Fibrosis Stage</td>
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</table>

#### Fibrosis Interpretation

<table>
<thead>
<tr>
<th>FibroTest Score</th>
<th>Metavir Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.21</td>
<td>F0 no fibrosis</td>
</tr>
<tr>
<td>0.22-0.27</td>
<td>F0-F1</td>
</tr>
<tr>
<td>0.28-0.31</td>
<td>F1 minimal fibrosis</td>
</tr>
<tr>
<td>0.32-0.48</td>
<td>F1-F2</td>
</tr>
<tr>
<td>0.49-0.58</td>
<td>F2 moderate fibrosis</td>
</tr>
<tr>
<td>0.59-0.72</td>
<td>F3 advanced fibrosis</td>
</tr>
<tr>
<td>0.73-0.74</td>
<td>F3-F4</td>
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<tr>
<td>0.75-1.00</td>
<td>F4 severe fibrosis</td>
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</table>

<table>
<thead>
<tr>
<th>Necroinflammat Act Score</th>
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</thead>
<tbody>
<tr>
<td>Necroinflammat Act Grade</td>
<td>No reference range available</td>
</tr>
<tr>
<td>Necroinflamat Interp</td>
<td>ActiTest Score</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>0.00-0.17</td>
<td>A0 no activity</td>
</tr>
<tr>
<td>0.18-0.29</td>
<td>A0-A1</td>
</tr>
<tr>
<td>0.30-0.36</td>
<td>A1 minimal activity</td>
</tr>
<tr>
<td>0.37-0.52</td>
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<tr>
<td>0.53-0.60</td>
<td>A2 significant activity</td>
</tr>
<tr>
<td>0.61-0.62</td>
<td></td>
</tr>
<tr>
<td>0.63-1.00</td>
<td>A3 severe activity</td>
</tr>
</tbody>
</table>

Not established > or = 18 Years: 106-279 mg/dL Haptoglobin Not established > or = 18 Years: 43-212 mg/dL Apolipoprotein A-1 Males: 94-176 mg/dL, Females: 101-198 mg/dL Total Bilirubin 2-9 Years: 0.2-0.8 mg/dL, 10-19 Years: 0.2-1.1 mg/dL > or = 20 Years: 0.2-1.2 mg/dL GGT Males: 8-32 U/L, 16-19 Years: 9-31 U/L, 20-29 Years: 3-70 U/L 30-39 Years: 3-90 U/L 40-54 Years: 3-95 U/L 55-59 Years: 3-85 U/L > or = 60 Years: 3-70 U/L Females: 2-12 Years: 3-22 U/L, 13-15 Years: 7-18 U/L 16-19 Years: 6-26 U/L, 20-29 Years: 3-40 U/L 30-39 Years: 3-50 U/L 40-49 Years: 3-55 U/L 50-59 Years: 3-70 U/L > or = 60 Years: 3-65 U/L Alanine Aminotransferase (ALT) Males: 2-3 Years: 5-30 U/L, 4-12 Years: 8-30 U/L, 13-15 Years: 7-32 U/L, 16-19 Years: 8-46 U/L > or = 20 Years: 9-46 U/L Females: 2-3 Years: 5-30 U/L, 4-12 Years: 8-24 U/L, 13-15 Years: 5-32 U/L 16-19 Years: 5-32 U/L > or = 20 Years: 6-29 U/L The reliability of results is dependent on compliance with the pre-analytical and analytical conditions recommended by BioPredictive. The Tests have to be deferred for: acute hemolysis, acute hepatitis, acute inflammation, extra hepatic cholestasis. The advice of a specialist should be sought for interpretation in chronic hemolysis and Gilbert's syndrome. The Test interpretation is not validated in liver transplant patients. Isolated extreme values of one of the components should lead to caution in interpreting the results. In case of discordance between a biopsy result and a Test, it is recommended to seek the advice of a specialist. The cause of these discordances could be due to a flaw of the Test or to a flaw in the biopsy; i.e. a liver biopsy has a 33% variability rate for one fibrosis stage. FibroTest is interpretable for chronic hepatitis B and C, alcoholic and non-alcoholic steatosis. ActiTest is interpretable for chronic hepatitis B and C.
**Clinical Information:** Autoimmune liver disease (eg, autoimmune hepatitis and primary biliary cirrhosis) is characterized by the presence of autoantibodies including smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA), and anti-liver/kidney microsomal antibodies type 1 (anti-LKM-1).(1) Subtypes of autoimmune hepatitis (AIH) are based on autoantibody reactivity patterns. Anti-LKM-1 antibodies serve as a serologic marker for AIH type 2 and typically occur in the absence of SMA and antinuclear antibodies. These antibodies react with a short linear sequence of the recombinant antigen cytochrome monooxygenase P450 2D6.(2) Patients with AIH type 2 more often tend to be young, female, and have severe disease that responds well to immunosuppressive therapy.

**Useful For:** Evaluation of patients with liver disease of unknown etiology Evaluation of patients with suspected autoimmune hepatitis

**Interpretation:** Seropositivity for anti-LKM-1 antibodies is consistent with a diagnosis of AIH type 2.

**Reference Values:**
- < or =20.0 Units (negative)
- 20.1-24.9 Units (equivocal)
- > or =25.0 Units (positive)

Reference values apply to all ages.


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**Lobster, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


FLBE 57946
Locust Black (Robinia pseudoacacia) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

LQTGP 63162
Long QT Syndrome Multi-Gene Panel, Blood

Clinical Information: Long QT syndrome (LQTS) is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on electrocardiogram (EKG), which may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. RWS has an estimated prevalence of 1 in 3,000 individuals. Of the families who meet clinical diagnostic criteria for RWS, approximately 75% have known genetic causes, while approximately 25% have no detectable pathogenic variants in any of the genes known to cause RWS. Approximately 3% of RWS cases are the result of large deletions or duplications in KCNQ1 or KCNH2. Deletions/duplications have not been reported in the other genes implicated in RWS. Only about half of the individuals with a pathogenic gene variant associated with RWS have symptoms, usually one to a few syncopal spells, and thus many patients with this condition unfortunately present with sudden cardiac death as their first symptom. Cardiac events may occur any time from infancy through adulthood, but are most common from the preteen years through the 20s. Additionally, RWS is believed to account for approximately 10% to 15% of sudden infant death syndrome (SIDS) cases. In some cases, LQTS may be associated with congenital profound bilateral sensorineural hearing loss, known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either KCNQ1 or KCNE1. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies that may include hand/foot syndactyly, structural heart defects, facial dysmorphism, and neurodevelopmental features. Ventricular tachyarrhythmia is the leading cause of death with an average age of death of 2.5 years. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the CACNA1C gene. Management strategies for LQTS include pharmacologic therapies, implantable cardioverter defibrillators (ICD), or other surgical interventions, and lifestyle restrictions such as avoidance of competitive sports or other triggers for cardiac events. In some cases, knowledge of the LQTS genotype may assist in tailoring an individual’s treatment plan. For example, patients with an SCN5A pathogenic variant may not respond well to the typical first-line therapy of beta-blockers and may have a lower threshold for consideration of an ICD. Genetic testing in LQTS is recommended and supported by multiple consensus statements to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death and, thus, EKG analysis alone is insufficient to rule out the diagnosis and genetic testing is necessary to confirm the presence or absence
of disease in at-risk family members. Pre- and post-test genetic counseling is an important factor in the diagnosis and management of LQTS and is supported by expert consensus statements.

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of long QT syndrome Establishing a diagnosis of a long QT syndrome, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**LORAZ**

**Lorazepam (Ativan), Serum**

**Reference Values:**
Reference Range: 50.0 - 240.0 ng/mL

**FUSF**

**Low-Grade Fibromyxoid Sarcoma (LGFMS), 16p11.2 (FUS or TLS) Rearrangement, FISH, Tissue**

**Clinical Information:** Low-grade fibromyxoid sarcoma (LGFMS) is a rare malignant soft tissue tumor characterized by a bland fibroblastic spindle cell proliferation arranged in alternating fibrous and cell rich areas. The tumor cells are typically small and have indistinct margins. The nuclei are oval to round and have a low nuclear-cytoplasmic ratio. Mitotic figures are rare. Immunohistochemical staining is usually negative for muscle markers and positive for vimentin and focally for cytokeratin. The tumor cells show strong expression of S100 protein and in some cases, CD68. The differential diagnosis includes fibromatosis, dermatofibrosarcoma protuberans, and other soft tissue sarcomas. The clinical course is variable, with some cases demonstrating a more indolent course while others may progress to high-grade sarcoma. Treatment options include surgery, radiation therapy, and chemotherapy. The prognosis is generally poor, with a tendency for local recurrence and metastasis to lymph nodes and distant sites. Long-term follow-up is necessary to detect late recurrences. The most common site of metastasis is the lung, followed by bone and liver. The overall survival rate is less than 50% at 5 years.
myxoid areas, with or without giant collagen rosettes. These tumors are characterized by the chromosome translocation t(7;16)(q33-34;p11), which results in the fusion of FUS (also called TLS) on chromosome 16 to CREB3L2 (also called BBF2H7) on chromosome 7. Greater than 70% of LGFMS are cytogenetically characterized by this translocation. In rare cases, a variant t(11;16)(p11;p11) has been described in which FUS is fused to CREB3L1 (OASIS), a gene structurally related to CREB3L2. Testing of FUS locus rearrangement should be concomitant with histologic evaluation, and positive results may support the diagnosis of LGFMS.

**Useful For:** Supporting the diagnosis of low-grade fibromyxoid sarcoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FUS probe set. A positive result is consistent with the diagnosis of low-grade fibromyxoid sarcoma (LGFMS). A negative result suggests that a FUS gene rearrangement is not present, but does not exclude the diagnosis of LGFMS.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
1. Fletcher CDM, Unni K, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC: Lyon 2002, pp 104-105

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**LOX**

**Loxapine (Loxitaner) and 8-Hydroxyloxapine**

**Reference Values:**
- **Loxapine:**
  - Reference Range: 5.0 - 30.0 ng/mL
- **8-Hydroxy-Loxapine:**
  - Reference Range: 20.0 - 100.0 ng/mL

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**LCAF**

**Lung Cancer, ALK (2p23) Rearrangement, FISH, Tissue**

**Clinical Information:** Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung carcinoma (NSCLC) accounts for 75% to 80% of all lung cancers with an overall 5-year survival rate of 10% to 15%. Standard chemotherapy regimens have had marginal success in improving clinical outcomes. Targeted treatments may be used as novel molecular changes are identified. Rearrangements of the ALK locus are found in a subset of lung carcinomas and their identification may guide important therapeutic decisions for the management of these tumors. The fusion of EML4 (echinoderm microtubule-associated protein-like 4) gene with the ALK (anaplastic large cell lymphoma kinase) gene results from an inversion of chromosome band 2p23. The ALK-EML4 rearrangement has been identified in 3% to 5% of NSCLC with the majority in adenocarcinoma and younger male patients who were light or nonsmokers. Lung cancers harboring ALK rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors, but may be highly sensitive to ALK inhibitors, like Xalkori (crizotinib). The drug Xalkori works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that Xalkori treatment of patients with tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression.

**Useful For:** Identifying patients with late-stage, non-small cell lung cancers who may benefit from...
treatment with the drug Xalkori

**Interpretation:** A positive result (ALK rearrangement identified) is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result suggests rearrangement of the ALK locus and a tumor that may be responsive to ALK inhibitor therapy. A negative result suggests no rearrangement of the ALK gene region at 2p23. A specimen is considered positive if >50% demonstrate a signal pattern consistent with an ALK rearrangement and considered negative if <10% of cells are positive. If the results are equivocal (>10% and <50%), an additional 50 cells are scored and would be considered positive if >15% of cells exhibit a signal pattern consistent with an ALK rearrangement and negative if <15% of cells exhibit an ALK rearrangement.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**Lung Cancer, EGFR with ALK Reflex, Tumor**

**Clinical Information:** Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung carcinoma (NSCLC) accounts for 75% to 80% of all lung cancers with an overall 5-year survival rate of 10% to 15%. Standard chemotherapy regimens have had marginal success in improving clinical outcomes. Epidermal growth factor receptor (EGFR) is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. EGFR-targeted therapies (eg, gefitinib and erlotinib) have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to traditional chemotherapy. EGFR tyrosine kinase inhibitors have also been shown to increase progression-free and overall survival in patients who receive these therapies as a first-line therapy for the treatment of NSCLC. Agents such as gefitinib and erlotinib, which prevent ATP binding to EGFR kinase, do not appear to have any meaningful inhibitor activity on tumors that lack an activating EGFR mutation or in tumors that demonstrate the presence of drug-resistant EGFR mutations (eg, exon 20 insertions and T790M). Therefore, current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I, or small deletions within exon 19 and the absence of drug-resistant mutations. As a result, the mutation status of EGFR is a critical marker for selecting patients for EGFR-targeted therapy. Rearrangements of the anaplastic lymphoma kinase (ALK) locus are found in a subset of lung carcinomas (generally EGFR wild-type tumors) and their identification by FISH may guide important therapeutic decisions for the management of these tumors. The fusion of the EML4 (echinoderm microtubule-associated protein-like 4) gene with the ALK (anaplastic large cell lymphoma kinase) gene results from an inversion of chromosome band 2p23. The ALK-EML4 rearrangement has been identified in 3% to 5% of NSCLC with the majority occurring in adenocarcinoma and younger male patients who were light or nonsmokers. Recent studies have demonstrated that lung cancers harboring ALK rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors, but may be highly sensitive to ALK inhibitors, like crizotinib (Xalkori). The drug crizotinib works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that crizotinib treatment of patients with tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression. The ALK/EML4 FISH assay is an FDA-approved companion diagnostic test for crizotinib, which was recently approved by the FDA to treat certain patients with late-stage (locally advanced or metastatic), non-small cell lung cancers that harbor ALK gene rearrangements. It is useful for the identification of lung cancer patients who will benefit from crizotinib.
therapy.

**Useful For:** Identifying non-small cell lung cancers that may benefit from treatment with epidermal growth factor receptor-tyrosine kinase or anaplastic lymphoma kinase inhibitors

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

---

**Lung Cancer, RET (10q11) Rearrangement, FISH, Tissue**

**Clinical Information:** Lung cancer is the leading cause of cancer mortality in developed countries. The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK rearrangements and EGFR mutations, respectively. Abnormalities of the RET proto-oncogene at chromosome 10q11 have been identified as the causative genetic abnormality in the neoplasia predisposition syndrome multiple endocrine neoplasia type II (MEN2), as well as in thyroid carcinomas. Recently, chromosomal rearrangements of RET have been identified in a subset of lung adenocarcinomas. Patients with tumors harboring RET rearrangements may benefit from RET kinase inhibitors, but the clinical benefits of the inhibitor has not yet been clarified.

**Useful For:** Identifying RET gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for EGFR mutations and ALK rearrangements

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the RET locus and a tumor that may be responsive to RET kinase inhibitor therapy. A negative result suggests no rearrangement of the RET gene region at 10q11.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

---

**Lung Cancer, ROS1 (6q22) Rearrangement, FISH, Tissue**

**Clinical Information:** Lung cancer is the leading cause of cancer mortality in developed countries. The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK...
rearrangements and EGFR mutations, respectively. The c-ros oncogene 1 (ROS1), originally described in glioblastomas, has been identified as a potential relevant therapeutic target in lung adenocarcinoma. Crizotinib has shown in vitro activity and early evidence of clinical activity in ROS1-rearranged tumors.

**Useful For:** Identifying ROS1 gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for EGFR mutations and ALK rearrangements

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the ROS1 locus and a tumor that may be responsive to ALK-inhibitor therapy. A negative result suggests no rearrangement of the ROS1 gene region at 6q22.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

---

**LUPN 82613**

**Lupin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

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5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive  Reference values  apply to all ages.


FLUPV
91714

Lupus Anticoagulant Evaluation with Reflex

Reference Values:
Lupus Anticoagulant  Not Detected

This interpretation is based on the following test results:

PTT-LA Screen  < or = 40 seconds
DRVVT Screen   < or = 45 seconds

LUPPR
83092

Lupus Anticoagulant Profile

Clinical Information: Lupus anticoagulant (LAC) is an antibody to negatively charged phospholipid that interferes with phospholipid-dependent coagulation tests. LAC is found in, but not limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune disorders and collagen vascular disease, and occurs in response to medications or certain infections (eg, respiratory tract infections in children) and in individuals with no obvious underlying disease. LAC has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LAC may be at risk for bleeding.

Useful For: Confirming or excluding presence of lupus anticoagulant (LAC) distinguishing LAC from specific coagulation factor inhibitors and nonspecific inhibitors Investigation of a prolonged activated thromboplastin time, especially when combined with other coagulation studies

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
PROTHROMBIN TIME (PT)
  10.3-12.8 seconds

INR
  0.9-1.2
  The INR is used only for patients on stable oral anticoagulant therapy. It makes no significant contribution to the diagnosis or treatment of patients whose PT is prolonged for other reasons.

ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)
  Adults: 26-36 seconds
  The normal full-term newborn APTT may be up to 35% longer than in adults and even longer (up to twice the adult upper limit) in healthy premature infants. Typically, the APTT is in the adult reference range by age 3 months in healthy full-term infants and by age 6 months in healthy premature infants (30-60 weeks gestation)*.
  26-36 seconds (>3-6 months)
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

DILUTE RUSSELL'S VIPER VENOM TIME
  <1.2

Luteinizing Hormone (LH), Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). The alpha subunit of LH, follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), and human chorionic gonadotropin (hCG) are identical and contain 92 amino acids. The beta subunits of these hormones vary and confer the hormones' specificity. LH has a beta subunit of 121 amino acids and is responsible for interaction with the LH receptor. This beta subunit contains the same amino acids in sequence as the beta subunit of hCG and both stimulate the same receptor, however, the hCG beta subunit contains an additional 24 amino acids, and the hormones differ in the composition of their sugar moieties. Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, FSH and LH, from the anterior pituitary. In both males and females, LH is essential for reproduction. In females, the menstrual cycle is divided by a midcycle surge of both LH and FSH into a follicular phase and a luteal phase. This "LH surge" triggers ovulation thereby not only releasing the egg, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first 2 weeks. In case of pregnancy, luteal function will be further maintained by the action of hCG (a hormone very similar to LH) from the newly established pregnancy. LH supports thecal cells in the ovary that provide androgens and hormonal precursors for estradiol production. LH in males acts on testicular interstitial cells of Leydig to cause increased synthesis of testosterone.

Useful For: An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

Interpretation: In both males and females, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Postmenopausal LH levels are generally >40 IU/L. (Note: FSH is the preferred test to confirm menopausal status.) FSH and LH are generally elevated in: - Primary gonadal failure - Complete testicular feminization syndrome - Precocious puberty (either idiopathic or secondary to a central nervous system lesion) - Menopause - Primary ovarian hypodysfunction in females - Polycystic ovary disease in females - Primary hypogonadism in males LH is decreased in: - Primary ovarian hyperfunction in females - Primary hypergonadism in males FSH and LH are both decreased in failure of the pituitary or hypothalamus.

Reference Values:

Males

<table>
<thead>
<tr>
<th>Age/Stage</th>
<th>LH (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 days</td>
<td>not established</td>
</tr>
<tr>
<td>15 days</td>
<td>0.3-2.8</td>
</tr>
<tr>
<td>11 years</td>
<td>0.3-1.8</td>
</tr>
<tr>
<td>12 years</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>13 years</td>
<td>0.3-6.0</td>
</tr>
<tr>
<td>14 years</td>
<td>0.5-7.9</td>
</tr>
<tr>
<td>15-16 years</td>
<td>0.5-10.8</td>
</tr>
<tr>
<td>17 years</td>
<td>0.9-5.9</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>1.8-8.6</td>
</tr>
</tbody>
</table>

TANNER STAGES*

<table>
<thead>
<tr>
<th>Stage</th>
<th>LH (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.3-2.7</td>
</tr>
<tr>
<td>II</td>
<td>0.3-5.1</td>
</tr>
<tr>
<td>III</td>
<td>0.3-6.9</td>
</tr>
<tr>
<td>IV</td>
<td>0.5-5.3</td>
</tr>
<tr>
<td>V</td>
<td>0.8-11.8</td>
</tr>
</tbody>
</table>

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*Puberty onset occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females
0-14 days: not established
15 days-3 years: 0.3-2.5 IU/L
4-6 years: < or =1.9 IU/L
7-8 years: < or =3.0 IU/L
9-10 years: < or =4.0 IU/L
11 years: < or =6.5 IU/L
12 years: 0.4-9.9 IU/L
13 years: 0.3-5.4 IU/L
14 years: 0.5-31.2 IU/L
15 years: 0.5-20.7 IU/L
16 years: 0.4-29.4 IU/L
17 years: 1.6-12.4 IU/L
> or =18 years
Premenopausal
Follicular: 2.1-10.9 IU/L
Midcycle: 20.0-100.0 IU/L
Luteal: 1.2-12.9 IU/L
Postmenopausal: 10.0-60.0 IU/L

TANNER STAGES*
Stage I: < or =2.0 IU/L
Stage II: < or =6.5 IU/L
Stage III: 0.3-17.2 IU/L
Stage IV: 0.5-26.3 IU/L
Stage V: 0.6-13.7 IU/L

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.


**LUXO**

**Luxol Fast Blue/PAS, Nrv ST**

Reference Values:
Report sent under separate cover

**PBORR**

**Lyme Disease (Borrelia burgdorferi), Molecular Detection, PCR**

Clinical Information: Lyme disease is a multisystem and multistage infection caused primarily by 3 species of tick-borne spirochetes in the Borrelia burgdorferi sensu lato genogroup. These spirochetes include Borrelia burgdorferi sensu stricto (North America and Western Europe), Borrelia afzelii (Central and Western Europe and Russia), and Borrelia garinii (Europe, Russia, and northern Asia). Endemic areas
for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes scapularis (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease is the most commonly reported tick-borne infection in Europe and North America (CDC). Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema (chronicum) migrans (ECM), a unique expanding skin lesion with central clearing that has a ring-like appearance, is typically the first stage of the disease. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. Serology is currently the diagnostic method of choice for Lyme disease. However, serology may not be positive until 2 to 4 weeks after onset of ECM, and direct detection of Borrelia species. Target DNA using PCR may be a useful adjunct to existing diagnostic tests for acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of ECM lesions, as well as DNA from synovial and cerebrospinal fluid in late-stage disease.(1) Borrelia DNA can also, rarely, be detected from blood, but is not the test of choice from this source. Lyme PCR may be useful for adjunctive testing to support a serologic diagnosis of Lyme disease, and should be performed in conjunction with FDA-approved serologic tests. PCR results should be correlated with serologic and epidemiologic data and clinical presentation of the patient.

**Useful For:** Confirmation of active Lyme disease Supporting the diagnosis of Lyme arthritis Testing of cerebrospinal fluid (CSF) by PCR in patients with suspected Lyme neuroborreliosis should be requested only on patients with positive Borrelia burgdorferi antibody in serum confirmed by Western blot assay LYWB / Lyme Disease Antibody, Immunoblot, Serum and with abnormal CSF findings (elevated protein and WBC >10 cells/high-power field).

**Interpretation:** A positive result indicates the presence of DNA from Borrelia burgdorferi, the agent of Lyme disease. A negative result indicates the absence of detectable DNA from Borrelia burgdorferi in the specimen. Due to the clinical sensitivity limitations of the PCR assay, a negative result does not preclude the presence of the organism or active Lyme disease.

**Reference Values:**

Negative

**Clinical References:**


**Lyme Disease (Borrelia burgdorferi), Molecular Detection, PCR, Blood**

**Clinical Information:** Lyme disease is a multisystem and multistage infection caused by 3 species of tick-borne spirochetes in the Borrelia burgdorferi sensu lato genogroup. These spirochetes include Borrelia burgdorferi sensu stricto (North America and Western Europe), Borrelia afzelii (Central and Western Europe and Russia), and Borrelia garinii (Europe, Russia, and northern Asia). Endemic areas for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema (chronicum) migrans (ECM), a unique expanding skin lesion with central clearing resulting in a ring-like appearance, is the first stage of the disease. Any of the following clinical manifestations may be present in patients with Lyme disease: arthritis, neurological disease, cardiac disease, or skin lesions. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur
even though the patient does not recall a tick bite or a rash. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Treatment with penicillin, tetracycline, erythromycin, chloramphenicol, or ceftriaxone is considered appropriate therapy. Serology is currently the diagnostic method of choice for Lyme disease. The Second National Conference on the Serologic Diagnosis of Lyme Disease (1994) recommended that laboratories use a 2-test approach for the serologic diagnosis of Lyme disease. Accordingly, specimens are first tested by the more sensitive EIA or enzyme-linked immunosorbent assay (ELISA). A Western blot (WB) assay is used to confirm positive Lyme EIA or ELISA results due to the presence of IgG- or IgM-class antibodies. WB identifies the specific proteins to which the patient's antibodies bind. Although there are no proteins that specifically diagnose Borrelia burgdorferi infection, the number of proteins recognized in the WB assay is correlated with diagnosis. Since serology may not be positive until 2 to 4 weeks after onset of ECM, direct detection of Borrelia burgdorferi-specific target DNA sequences using PCR is a promising adjunct to existing diagnostic tests. PCR has shown utility for detection of Borrelia burgdorferi DNA from skin biopsies of ECM lesions, and from synovial and cerebrospinal fluid in late-stage disease. Borrelia burgdorferi DNA can also, rarely, be detected from blood, but is not the test of choice from this source.

**Useful For:** Confirmation of active Lyme disease Monitoring Lyme disease treatment PCR testing should be limited to patients with a positive, or at least an equivocal, serologic test for antibody to Borrelia burgdorferi.

**Interpretation:** A positive result indicates the presence of DNA from Borrelia burgdorferi, the agent of Lyme disease. A negative result indicates the absence of detectable DNA from Borrelia burgdorferi in the specimen. Due to the diagnostic sensitivity limitations of the PCR assay, a negative result does not preclude the presence of the organism or active Lyme disease.

**Reference Values:**

Negative

**Clinical References:**


**FBBAB Lyme Disease Antibody Index for CNS Infection**

**Reference Values:**

Lyme Disease Antibody Index:

< or = 1.0  Negative
1.1 - 1.2     Equivocal
> or = 1.3  Positive

Control Antibody Index: < or = 1.0

Albumin Ratio: <0.0078

The Lyme Disease Antibody Index is used as an aid for the diagnosis of neuroborreliosis. An increased Lyme Disease Antibody Index (>1.2), accompanied by a Control Antibody Index of less than 1.0 and an Albumin Ratio of less than 0.0078, is strong evidence for intrathecal synthesis of organism-specific antibody, and thus CNS B. burgdorferi infection. Elevation of either the control antibody index, the Albumin Ratio, or both may indicate leakage of antibody across the blood-brain barrier which may falsely elevate the Lyme Disease Antibody Index.
**Lyme Disease Antibody, Immunoblot, Serum**

**Clinical Information:** Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States (US) correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema chronicum migrans (ECM), a unique expanding skin lesion with central clearing that results in a ring-like appearance, is the first stage of the disease. Any of the following clinical manifestations may be present in patients with Lyme disease: arthritis, neurological or cardiac disease, or skin lesions. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall having a tick bite or a rash. According to the manufacturers package insert, early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. However, the early administration of antibiotics may suppress the antibody response to levels that are undetectable by current laboratory tests. (1) The Second National Conference on the Serologic Diagnosis of Lyme Disease (1994) recommended that laboratories use a 2-test approach for the serologic diagnosis of Lyme disease. Accordingly, specimens are first tested by the more sensitive EIA. An immunoblot assay is used to supplement positive or equivocal Lyme (EIA). An immunoblot identifies the specific proteins to which the patient's antibodies bind. Although there are no proteins that specifically diagnose Borrelia burgdorferi infection, the number of proteins recognized in the immunoblot assay is correlated with diagnosis. Culture or PCR of skin biopsies obtained near the margins of ECM are frequently positive. In late (chronic) stages of the disease, serology is often positive and the diagnostic method of choice. PCR testing also may be of use in these late stages if performed on synovial fluid or cerebrospinal fluid.

**Useful For:** Diagnosing Lyme disease IgM assay is useful for confirming stage 1 (acute) Lyme disease. IgG assay is useful for confirming stage 2 and stage 3 Lyme disease.

**Interpretation:** IgM: IgM antibodies to Borrelia burgdorferi may be detectable within 1 to 2 weeks following the tick bite; they usually peak during the third to sixth week after disease onset, and then demonstrate a gradual decline over a period of months. IgM antibody may persist for months even though antimicrobial agents are given. The IgM assay is more likely to be useful during early disease, and should only be tested during the first 4 to 6 weeks after disease onset. Negative specimens typically demonstrate antibodies to less than 2 of the 3 significant Borrelia burgdorferi proteins. Additional specimens should be submitted in 2 to 3 weeks if Borrelia burgdorferi exposure has not been ruled out. Individuals who have recently seroconverted due to infection with Borrelia burgdorferi may display incomplete banding patterns, but may develop increased reactivity (both in band intensity and number) when followed for a period of 4 to 6 months. IgG: Serum IgG is detected as early as 2 weeks after onset of disease. Significant concentrations of antibody and immunoblot banding patterns for Borrelia burgdorferi can be found years after onset. Normal specimens and false-positive EIA specimens generally have antibodies to 4 or fewer proteins. Except for early patients, antibodies from patients with Lyme disease generally bind to 5 or more proteins. For persons who have received recombinant OspA vaccine and who are not infected with Borrelia burgdorferi, an intense band representing antibody to the OspA protein (band 30) should be visible on the immunoblot.

**Reference Values:**
IgG: negative
IgM: negative

Lyme Disease Antibody, Immunoblot, Spinal Fluid

Clinical Information: Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States (US) correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Any of the following clinical manifestations may be present in patients with Lyme disease: skin lesions or cardiac or neurological disease. In the first stage of disease, inflammation around the tick bite causes skin lesions, erythema chronicum migrans (ECM)-a unique expanding skin lesion with central clearing that results in a ring-like appearance. Culture of skin biopsies obtained near the margins of ECM are frequently positive. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall a tick bite or rash. The presence of antibodies to Borrelia burgdorferi in cerebrospinal fluid (CSF) is suggestive of neurologic Lyme disease (Lyme neuroborreliosis). PCR testing also may be used to confirm late-stage neurologic disease. However, the sensitivity of PCR is low when testing CSF. According to the manufacturer’s package insert, early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. However, the early administration of antibiotics may suppress the antibody response to levels that are undetectable by current laboratory tests.(1)

Useful For: Supplementing positive Lyme disease antibody screen (EIA) results and serving as an aid in the serologic diagnosis of Lyme neuroborreliosis

Interpretation: Currently no criteria exist for the interpretation of immunoblot testing on cerebrospinal fluid. The presence of any bands may represent either intrathecal antibody production or passive transfer of antibody from blood.

Reference Values:
IgG: none detected
IgM: none detected


Lyme Disease Serology, Serum

Clinical Information: Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States (US) correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema chronicum migrans (ECM), a unique expanding skin lesion with central clearing that results in a ring-like appearance, is the first stage of the disease. Any of the following clinical manifestations may be present in patients with Lyme disease: arthritis, neurological disease, cardiac disease, or skin lesions. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall a tick bite or a rash. Serology may not be positive until 2 to 4 weeks after onset of ECM; however, culture of skin biopsies obtained near the margins of ECM are frequently positive. In late (chronic) stages of the disease, serology is often positive and the diagnostic method of choice. PCR testing also may be of use in these late stages if performed on synovial or cerebrospinal fluid. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Treatment with penicillin, tetracycline, erythromycin,
chloramphenicol, or ceftriaxone is considered appropriate therapy. The Second National Conference on the Serologic Diagnosis of Lyme Disease (1994) recommended that laboratories use a 2-test approach for the serologic diagnosis of Lyme disease. Accordingly, specimens are first tested by the more sensitive EIA or enzyme-linked immunosorbent assay (ELISA). A Western blot (WB) assay is used to confirm positive Lyme EIA or ELISA results due to the presence of IgG or IgM class antibodies. WB identifies the specific proteins to which the patient's antibodies bind. Although there are no proteins that specifically diagnose Borrelia burgdorferi infection, the number of proteins recognized in the WB assay is correlated with diagnosis.

**Useful For:** Diagnosing Lyme disease As a sensitive screening (enzyme-linked immunosorbent assay) test for Lyme disease

**Interpretation:** Negative result: no antibody to Borrelia burgdorferi detected. This result does not exclude the possibility of Borrelia burgdorferi infection. Patients in early stages of infection may not produce detectable levels of antibody. According to the manufacturer’s package insert, antibiotic therapy in early disease may prevent antibody production from reaching detectable levels. Patients with clinical history and/or symptoms suggestive of Lyme disease or where early Lyme disease is suspected, but with negative test results should be retested in 2 to 4 weeks. Equivocal result: the imprecision inherent in any method implies a lower degree of confidence in the interpretation of specimens with absorbance values very close to the calculated cutoff value. For this reason an equivocal category has been designated. Equivocal specimens will be tested by Western blot (WB) assays in accordance with Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories (APHL) recommendations. Positive result: antibody to Borrelia burgdorferi detected. All positive results will be supplemented by retesting the serum by WB for the detection of IgG and IgM antibodies to Borrelia burgdorferi, in accordance with CDC/APHL recommendations.

**Reference Values:**

**Clinical References:**

**CLYME**

**Lyme Disease Serology, Spinal Fluid**

**Clinical Information:** Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States (US) correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Any of the following clinical manifestations may be present in patients with Lyme disease: skin lesions, cardiac disease, or neurological disease. In the first stage of disease, inflammation around the tick bite causes skin lesions, erythema chronicum migrans (ECM)-a unique expanding skin lesion with central clearing that results in a ring-like appearance. Culture of skin biopsies obtained near the margins of ECM are frequently positive. Neurologic and cardiac symptoms may appear with stage 2, and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall a tick bite or rash. The presence of cerebrospinal fluid antibodies to Borrelia burgdorferi is indicative of neurologic Lyme disease (Lyme neuroborreliosis). PCR testing also may be used to confirm late-stage neurologic disease. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Treatment with beta lactams such as amoxicillin, cefixime or ceftriaxone, or doxycycline are considered the most appropriate therapy.

**Useful For:** Aiding in the diagnosis of Lyme neuroborreliosis
**Interpretation:** Intrathecal synthesis of antibody to Borrelia burgdorferi is indicative of neurological Lyme disease.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

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**Lymphocyte Proliferation Panel for Mitogens and Antigens**

**Clinical Information:** Several classes of ligands are capable of inducing blastogenesis and stimulating proliferation of lymphocytes in vitro, including plant mitogens (phytohemagglutinin [PHA], pokeweed [PWM], and concanavalin A [Con A]), bacterial products and superantigens (potent bacterial toxins that at low concentrations have the ability to activate large numbers of T cells), and phorbol esters. Cellular proliferation follows a complex series of signals that begins with engagement of lymphocyte surface receptors by a mitogenic or antigenic ligand. Subsequent signals, including gene activation and secretion of cytokines, result in synthesis of DNA and cell division. Measurement of mitogen-induced lymphocyte proliferation in vitro provides a semiquantitative assessment of total cell-mediated immunity.(1) The proliferative responses to PHA and Con A involve T lymphocytes, and the response to PWM involves both T and B lymphocytes in a T-dependent manner. Diminished proliferative responses to lectin mitogens occur in a variety of primary and secondary immunodeficiency diseases including diseases that affect T lymphocytes, B lymphocytes, and T and B lymphocytes.(2) Specific antigen recognition involves T-cell receptor recognition of specific peptide in the context of the appropriate MHC molecule on an antigen-presenting cell. T cells activate and proliferate in response to specific antigenic stimulus. The recall antigens (eg, Candida albicans and tetanus toxoid) are used to assess antigen-specific T-cell responses. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(3) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(4-6) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(4) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening (7), and during summer compared to winter.(8) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:**
Evaluating patients suspected of having diminished cellular immune function Evaluating patients with primary and secondary immunodeficiency diseases that affect T lymphocytes, including combined immunodeficiency diseases (eg, severe combined immunodeficiency, cellular immunodeficiency diseases, and some patients with humoral immunodeficiency diseases (eg, common variable immunodeficiency) Evaluating functional T-cell recovery post-hematopoietic stem cell transplant or immunosuppressive therapy for solid-organ transplantation or in other clinical contexts

**Interpretation:** Diminished responses to lectin mitogens and/or antigens may be consistent with a primary or secondary immunodeficiency disease. Abnormal results are not specific for a particular disease, and the magnitude of the abnormality is not necessarily related to the degree of immunodeficiency. In the case of antigen-specific proliferative responses, it is possible to have low or absent responses if a long interval has passed since the original or booster vaccination (tetanus toxoid).

**Reference Values:**
LYMPHOCYTE PROLIFERATION TO ANTIGENS
Viability of lymphocytes at day 0: ≥ 75.0%
Maximum proliferation of Candida albicans as % CD45: ≥ 5.7%
Maximum proliferation of Candida albicans as % CD3: > or =3.0%
Maximum proliferation of tetanus toxoid as % CD45: > or =5.2%
Maximum proliferation of tetanus toxoid as % CD3: > or =3.3%

LYMPHOCYTE PROLIFERATION TO MITOGENS
Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of phytohemagglutinin as % CD45: > or =49.9%
Maximum proliferation of phytohemagglutinin as % CD3: > or =58.5%
Maximum proliferation of pokeweed mitogen as % CD45: > or =4.5%
Maximum proliferation of pokeweed mitogen as % CD3: > or =3.5%
Maximum proliferation of pokeweed mitogen as % CD19: > or =3.9%

Clinical References:

Lymphocyte Proliferation to Anti-CD3/Anti-CD28 and Anti-CD3/Interleukin-2 (IL-2) by Flow Cytometry

Clinical Information: T-cell stimulation in vitro is used extensively in the diagnostic immunology arena for facilitating T-cell proliferation and evaluation of T-cell function in a variety of clinical contexts.(1,2) The widely used method for assessing lymphocyte proliferation has been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1) the technique is cumbersome due to the use of radioactivity; 2) it does not allow discrimination of responding cell populations in response to stimulation; and 3) it does not provide any information on the contribution of apoptosis or cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation, decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and underrepresentation of T cells in the peripheral blood mononuclear cell pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or sample. While mitogens such as phytohemagglutinin (PHA) activate T cells by binding to cell membrane glycoproteins, including the T-cell receptor (TCR)-CD3 complex, there are a number of mitogenic or comitogenic antibodies, including those directed against the CD3 coreceptor that can stimulate T-cell proliferation. Typically, anti-CD3 antibodies provide an initial activation signal, but do not induce significant proliferation, and the addition of a costimulatory antibody (anti-CD28) provides the stimulus for robust proliferation.(3) An exogenous T-cell growth factor, such as interleukin-2 (IL-2), may also be used as an alternate to anti-CD28 costimulation, and in patients with suspected IL-2 receptor-associated signaling defects, it may be more helpful than the use of anti-CD28. IL-2, an autocrine cytokine, has been demonstrated to be critical in T-cell proliferation.(4,5) The interaction of IL-2 with the IL-2 receptor (IL-2R) plays a central role in regulation of T-cell proliferation.(4) Triggering of the TCR leads to synthesis of IL-2 in certain T-cell subsets and induction of high-affinity IL-2Rs in antigen- or mitogen-activated T cells, and the
binding of IL-2 to IL-2R ultimately leads to T-cell proliferation. The use of exogenous IL-2 in association with anti-CD3 allows discrimination of whether T cells, which cannot proliferate to other mitogenic stimuli, can respond to a potent growth factor such as IL-2. Stimulation of T cells with soluble antibodies to anti-CD3 (and the associated TCR complex) causes mobilization of cytoplasmic calcium and translocation of protein kinase C from the cytoplasm to the cell membrane. This stimulation also causes induction of phosphatidylinositol metabolism and subsequent IL-2 production for proliferation.(6) T-cell activation induced by anti-CD3 antibody requires prolonged stimulation of protein kinase C, which apparently can be achieved by the concomitant use of the anti-CD28 antibody for costimulation without addition of other mitogenic stimuli, such as phorbol myristate acetate (PMA).(7) For this assay, we use a method that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. In the Invitrogen Click-iT-EdU assay, the click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. The Click-iT-EdU assay has been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(8) In the assay, an alkyn-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry.(9) Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK)-cell counts, on the other hand, is constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, the numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing, and consistency in timing, of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** A second-level test after lymphocyte proliferation to mitogens (specifically phytohemagglutinin) has been assessed. The anti-CD3 proliferation panel is not a first-level test for assessing lymphocyte (T-cell) function. Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency [SCID], etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation Evaluation of T-cell function in patients receiving immunosuppressive or immunomodulatory therapy Evaluation of T-cell function in the context of identifying neutralizing antibodies in patients receiving therapeutic anti-CD3 antibody immunosuppression for solid organ transplantation or autoimmune diseases, such as type 1 diabetes

**Interpretation:** Abnormal test results to anti-CD3/aCD28/interleukin-2 (IL-2) stimulation are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with underrepresentation of T cells within the peripheral blood mononuclear cells (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. The evaluation of T-cell proliferation to anti-CD3/IL-2 is likely to be helpful in assessing T-cell function in patients with refractory responses to other mitogenic and antigenic stimuli, specifically in the context of IL-2-receptor signaling defects, enabling greater mechanistic insight into the origins of T-cell dysfunction. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to any mitogenic stimulus, including
anti-CD3/anti-CD28, can be regarded as a more specific but less sensitive test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of identification of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age, and a continuing decline through adolescence to half the neonatal response.(10) In our evaluation of 43 pediatric samples (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for the mitogens, pokeweed mitogen (PWM) and phytohemagglutinin (PHA), respectively. Comparisons between pediatric and adult data have not been performed for anti-CD3/CD28 due to unavailability of prospective blood samples from healthy or patient pediatric donors for purposes of analytical validation. It should be noted that without obtaining formal pediatric reference values it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens (including anti-CD3 stimulation) and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed >24 and <48 hours post blood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

**Reference Values:**

Viability of lymphocytes at day 0: > or =75.0%

Maximum proliferation of anti-CD3 as % CD45: > or =19.4%

Maximum proliferation of anti-CD3 as % CD3: > or =20.3%

Maximum proliferation of anti-CD3 + anti-CD28 as % CD45: > or =37.5%

Maximum proliferation of anti-CD3 + anti-CD28 as % CD3: > or =44.6%

Maximum proliferation of anti-CD3 + IL-2 as % CD45: > or =41.7%

Maximum proliferation of anti-CD3 + IL-2 as % CD3: > or =46.2%

**Clinical References:**


LPAGF 60592 Lymphocyte Proliferation to Antigens, Blood

**Clinical Information:** Determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with recall antigens, including Candida albicans (CA) and tetanus toxoid (TT), has been part of the diagnostic immunology repertoire for many years.(1,2) The widely used method for assessing lymphocyte proliferation to antigens has hitherto been the measurement of
3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity 2. It does not allow discrimination of responding cell populations in response to stimulation 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and underrepresentation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or sample.

Antigens, like CA and TT, have been widely used to measure antigen-specific recall (anamnestic) T-cell responses when assessing cellular immunity. In fact, it may be more revealing about cellular immune compromise than assessing the response of lymphocytes to mitogens because the latter can induce T-cell proliferative responses even if those T cells are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to antigens are considered a diagnostically more sensitive, but less specific, test of aberrant T-cell function. (2) Antigens used in recall assays measure the ability of T cells bearing specific T-cell receptors (TCR) to respond to such antigens when processed and presented by antigen-presenting cells. The antigens used for assessment of the cellular immune response are selected to represent antigens, seen by a majority of the population, either through natural exposure (CA) or as a result of vaccination (TT). For this assay, we use a method that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-AAD and Annexin V. The Click-iT-EdU assay has already been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation. (3) The degree of impairment of antigen-specific T-cell responses can vary depending on the nature of the cellular immune compromise. For example, some, but not all, patients with partial DiGeorge syndrome, a primary cellular immunodeficiency, have been reported to have either decreased or absent T-cell responses to CA and TT. (4) Similarly, relative immune compromise, especially to TT, has been reported in children with vitamin A deficiency, but the measurements have been largely of the humoral immune response. Since this requires participation of the cellular immune compartment, it can be postulated that there could be a potential impairment of antigen-specific T-cell responses as well. (5)

Useful For: Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ transplant patients Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency: SCID, etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation

Interpretation: Abnormal test results to antigen stimulation are indicative of impaired T-cell function, if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a “dilution” effect with underrepresentation of T cells within the peripheral blood mononuclear cell (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. In the case of antigen-specific T-cell responses to tetanus toxoid (TT), there can be absent responses due to natural waning of cellular immunity, if the interval between vaccinations has exceeded the recommended period, especially in adults. In such circumstances, it would be appropriate to measure TT-specific T-cell responses 4 to 6 weeks after a booster vaccination. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to antigens can be regarded as a more sensitive, but less specific, test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of an opportunistic infection. Controls in this laboratory and most clinical laboratories are
healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. It is reasonable to expect robust T-cell-specific responses to TT in children without cellular immune compromise, as a result of repeated childhood vaccinations. The response to Candida albicans can be more variable depending on the extent of exposure and age of exposure. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. It should be noted that without obtaining formal pediatric reference values, it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls.

**Reference Values:**

Viability of lymphocytes at day 0:  > or = 75.0%

Maximum proliferation of Candida albicans as % CD45:  > or = 5.7%

Maximum proliferation of Candida albicans as % CD3:  > or = 3.0%

Maximum proliferation of tetanus toxoid as % CD45:  > or = 5.2%

Maximum proliferation of tetanus toxoid as % CD3:  > or = 3.3%

**Clinical References:**


**Lymphocyte Proliferation to Mitogens, Blood**

**Clinical Information:** The method of determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with mitogenic plant lectins (mitogens) such as phytohemagglutinin (PHA) and pokeweed mitogen (PWM) has been part of the diagnostic immunology repertoire for many years.(1,2) The widely used method for assessing lymphocyte proliferation has hitherto been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity 2. It does not allow discrimination of responding cell populations in response to stimulation 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under-representation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. Mitogens are very potent stimulators of T-cell activation and proliferation independent of their antigenic specificity.(3) It has been suggested that mitogens can induce T-cell proliferative responses even if they are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to mitogens are considered a diagnostically less sensitive but more specific test of aberrant T-cell function. Lectin mitogens have been shown to bind the T-cell receptor, which is glycosylated through its carbohydrate moiety, thereby activating quiescent T cells. Mitogenic stimulation has been shown to increase

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**Reference Values:**

Viability of lymphocytes at day 0: ≥75.0%

Maximum proliferation of Candida albicans as % CD45: ≥5.7%

Maximum proliferation of Candida albicans as % CD3: ≥3.0%

Maximum proliferation of tetanus toxoid as % CD45: ≥5.2%

Maximum proliferation of tetanus toxoid as % CD3: ≥3.3%

**Clinical References:**


**Lymphocyte Proliferation to Mitogens, Blood**

**Clinical Information:** The method of determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with mitogenic plant lectins (mitogens) such as phytohemagglutinin (PHA) and pokeweed mitogen (PWM) has been part of the diagnostic immunology repertoire for many years.(1,2) The widely used method for assessing lymphocyte proliferation has hitherto been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity 2. It does not allow discrimination of responding cell populations in response to stimulation 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under-representation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. Mitogens are very potent stimulators of T-cell activation and proliferation independent of their antigenic specificity.(3) It has been suggested that mitogens can induce T-cell proliferative responses even if they are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to mitogens are considered a diagnostically less sensitive but more specific test of aberrant T-cell function. Lectin mitogens have been shown to bind the T-cell receptor, which is glycosylated through its carbohydrate moiety, thereby activating quiescent T cells. Mitogenic stimulation has been shown to increase

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**Reference Values:**

Viability of lymphocytes at day 0: ≥75.0%

Maximum proliferation of Candida albicans as % CD45: ≥5.7%

Maximum proliferation of Candida albicans as % CD3: ≥3.0%

Maximum proliferation of tetanus toxoid as % CD45: ≥5.2%

Maximum proliferation of tetanus toxoid as % CD3: ≥3.3%
intracellular calcium (Ca++) in T cells, which is absolutely essential for T-cell proliferation. While PHA is a strong T-cell mitogen, PWM is a weak T-cell mitogen, but it also induces B-cell activation and proliferation as well. For this assay, we use a method that directly measures the S-phase proliferation of lymphocytes through the use of Click chemistry. In the Invitrogen Click-iT-EdU assay, the Click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. In the assay, an alkyn-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry.(4) Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-AAD and Annexin V. The Click-iT-EdU assay has already been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(5) The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK)-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing, and consistency in timing, of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ transplant patients Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency; SCID, etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation

**Interpretation:** Abnormal test results to mitogen stimulation are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with under-representation of T cells within the peripheral blood mononuclear cell (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to mitogens can be regarded as a more specific but less sensitive test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age, and a continuing decline through adolescence to half the neonatal response.(6) In our evaluation of 43 pediatric specimens (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for pokeweed (PWM) and phytohemagglutinin (PHA), respectively. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. It should be noted that without obtaining formal pediatric reference values it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or
controls. Lymphocyte proliferation responses to mitogens and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed >24 and <48 hours postblood collection, therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

**Reference Values:**
Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of phytohemagglutinin as % CD45: > or =49.9%
Maximum proliferation of phytohemagglutinin as % CD3: > or =58.5%
Maximum proliferation of pokeweed mitogen as % CD45: > or =4.5%
Maximum proliferation of pokeweed mitogen as % CD3: > or =3.5%
Maximum proliferation of pokeweed mitogen as % CD19: > or =3.9%


**64720 Lymphoid Enhancer-Binding Factor 1(LEF1), Immunostain Without Interpretation**

**Clinical Information:** Lymphoid enhancer-binding factor 1 (LEF1) is a transcription factor that participates in the activation of genes within the Wnt signaling pathway. LEF1 is expressed by inactive T cells and a subset of B cells.

**Useful For:** Differentiating cancers of B-cell origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required, order 70012 / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 1-855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**LSDX 62731 Lysergic Acid Diethylamide (LSD) Confirmation, Chain of Custody, Urine**

**Clinical Information:** Lysergic acid diethylamide (LSD) is an extremely potent psychedelic ergot alkaloid derived from the fungus, Claviceps purpurea.1 The drug LSD binds to serotonin receptors in the
Lysergic Acid Diethylamide (LSD) Confirmation, Urine

Clinical Information: Lysergic acid diethylamide (LSD) is an extremely potent psychedelic ergot alkaloid derived from the fungus, Claviceps purpurea.(1) The drug LSD binds to serotonin receptors in the central nervous system and acts as a serotonin agonist. The clearance half-life of LSD averages 3 to 4 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of LSD greater than the lower limit of quantification (LOQ; cutoff concentration) indicates exposure to LSD within 1 day.(2) LSD is metabolized to 2-oxo-3-hydroxy-LSD, which is present at concentrations 16 to 43 times higher than LSD, and is likely to be present in urine for up to 4 days after last exposure.(3,4) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Confirming use of lysergic acid diethylamide

Interpretation: Lysergic acid diethylamide (LSD) exposure is confirmed if LSD is present >0.5 ng/mL or if 2-oxo-3-hydroxy-LSD is present >5.0 ng/mL.

Reference Values:

Negative

Cutoff concentrations:

<table>
<thead>
<tr>
<th>Test</th>
<th>Cutoff Concentration</th>
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<tr>
<td>IMMUNOASSAY SCREEN</td>
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<tr>
<td>LSD BY LC-MS/MS</td>
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<tr>
<td>2-OXO-3-HYDROXY-LSD BY LC-MS/MS</td>
<td>&lt;5.0 ng/mL</td>
</tr>
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Clinical References:
Cutoff concentrations:

LSD BY LC-MS/MS
<0.5 ng/mL

2-OXO-3-HYDROXY-LSD BY LC-MS/MS
<5.0 ng/mL


LPCBS
61766
Lysophosphatidylincholines by Liquid Chromatography Tandem Mass Spectrometry (Reflex), Blood Spot

Reference Values:

<table>
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<tr>
<th>Analyte</th>
<th>Normal Range (mcg/mL)</th>
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<tbody>
<tr>
<td>C20 Lysophosphatidylincholine</td>
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</tr>
<tr>
<td>C22 Lysophosphatidylincholine</td>
<td>&lt; or =0.10</td>
</tr>
<tr>
<td>C24 Lysophosphatidylincholine</td>
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</tr>
<tr>
<td>C26 Lysophosphatidylincholine</td>
<td>&lt; or =0.20</td>
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</table>

LALB
62954
Lysosomal Acid Lipase, Blood

Clinical Information: Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by mutation in the LIPA gene. WD, the early onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, and hepatosplenomegaly. Peripheral blood lymphocytes are vacuolated and foam cells are present in the bone marrow. Approximately 50% of infants have adrenal calcifications. WD typically presents in the first weeks of life and is fatal in infancy. CESD, the late onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, leading to microvesicular steatosis and often liver failure. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides lead to premature atherosclerosis. Treatment options for WD and CESD have been limited but enzyme replacement therapy trials are now ongoing.

Useful For: Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency

Interpretation: Enzyme activity <1.5 nmol/h/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency; Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/h/mL) are not consistent with lysosomal acid lipase deficiency.
LALBS 62955

**Lysosomal Acid Lipase, Blood Spot**

**Clinical Information:** Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by mutation in the LIPA gene. WD, the early onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, and hepatosplenomegaly. Peripheral blood lymphocytes are vacuolated and foam cells are present in the bone marrow. Approximately 50% of infants have adrenal calcifications. WD typically presents in the first weeks of life and is fatal in infancy. CESD, the late onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, leading to microvesicular steatosis and often, liver failure. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides lead to premature atherosclerosis. Treatment options for WD and CESD have been limited but enzyme replacement therapy trials are now ongoing.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency

**Interpretation:** Enzyme activity <1.5 nmol/h/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency; Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/h/mL) are not consistent with lysosomal acid lipase deficiency.

**Reference Values:**

> or =21.0 nmol/h/mL


LDALD 64907

**Lysosomal and Peroxisomal Disorders Newborn Screen, Blood Spot**

**Clinical Information:** Lysosomes are intracellular organelles that contain hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease, which is inherited as an autosomal recessive lysosomal storage disorder, is caused by a deficiency of acid beta-glucosidase (glucocerebrosidase: GBA), resulting in increased storage of glucocerebroside (D-glucosylceramide). The deposition of glucocerebroside in macrophages of the reticuloendothelial system (Gaucher cells) causes organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease: -Type 1: adult/chronic -Type 2: acute neuropathic/infantile -Type 3: subacute
neuropathic/juvenile Type I, the most frequent form of the disease, is characterized by organomegaly, thrombocytopenia, and bone pain, and is frequent among the Ashkenazi Jewish population. Hepatosplenomegaly is usually present in all 3 types. Involvement of the central nervous system (CNS) is limited to the infantile type (type II). Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and/or chaperone therapy for types I and 3. Currently, only supportive therapy is available for type 2. Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase, which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Niemann-Pick types A and B are caused by mutations in the SMPD1 gene. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, eventually, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. Because Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, in particular the juvenile and adult-onset forms, is often considered late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment by enzyme replacement therapy became available recently, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by mutations in the GALT gene resulting in a deficiency of galactocerebrosidase (GALT, galactosylceramide alpha-galactosidase). Galactosylceramide (as with sulfated galacotosylceramide) is a lipid component of myelin. The absence of GALT results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Patients with this early infantile onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, has shown variable benefit. Fabry disease, caused by mutations in the GLA gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with <1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with >1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as
MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. MPS-I is caused by mutations in the IDUA gene and has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects such as Zellweger spectrum syndrome, are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants. X-linked adrenoleukodystrophy (XALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. At least 50% of all females who are heterozygotes for XALD are asymptomatic. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

**Useful For:** First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, MPSI, Niemann-Pick types A and B, and Pompe (Glycogen storage disorder type II) First-tier newborn screen for the peroxisomal disorder: X-linked adrenoleukodystrophy

**Interpretation:** An interpretive report is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Medical Laboratories or elsewhere, and a phone number to reach 1 of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

**Reference Values:**
Not applicable

Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot

Clinical Information: Lysosomes are intracellular organelles that contain hydrolytic enzymes to degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases where macromolecules accumulate due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. Accumulation of these macromolecules in the lysosomes leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease, which is inherited as an autosomal recessive lysosomal storage disorder, is caused by a deficiency of acid beta-glucosidase (glucocerebrosidase: GBA), resulting in increased storage of glucocerebroside (D-glucosylceramide). The deposition of glucocerebroside in macrophages of the reticuloendothelial system (Gaucher cells) causes organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease: -Type I: adult/chronic -Type II: acute neuropathic/infantile -Type III: subacute neuropathic/juvenile Type I, the most frequent form of the disease, is characterized by organomegaly, thrombocytopenia, and bone pain, and is frequent among the Ashkenazim. Hepatosplenomegaly is usually present in all 3 types. Involvement of the central nervous system (CNS) is limited to the infantile type (type II). Enzyme replacement therapy and/or substrate reduction therapy are available for patients with Gaucher disease type I. Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase, which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Sphingomyelinase is encoded by the SMPD1 gene. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, eventually, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. Because Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, when presenting as juvenile and adult-onset forms, is often diagnosed late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment with enzyme replacement therapy is available, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Patients with this early infantile onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly, and-based on newborn screening experience in New York-appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, is a treatment option with potential benefit. Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with <1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas,
Reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with >1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Enzyme replacement therapy is a treatment option for Fabry disease. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogens and bile acids. Peroxisome biogenesis defects such as Zellweger spectrum syndrome, are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to milder, later onset variants. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, and hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. X-linked adrenoleukodystrophy (XALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. At least 50% of all females who are heterozygotes for XALD are symptomatic. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of a lysosomal storage disorder, specifically Gaucher, Niemann-Pick type A or type B, Pompe, Krabbe, Fabry disease, or mucopolysaccharidosis I; or a peroxisomal disorder, either X-linked adrenoleukodystrophy or Zellweger syndrome spectrum

**Interpretation:** An interpretive report is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Medical Laboratories or elsewhere, and a phone number to reach 1 of the laboratory directors in case the referring physician has additional information.
questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

**Reference Values:**

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<thead>
<tr>
<th>Disease</th>
<th>Marker</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher</td>
<td>Acid Beta-Glucosidase</td>
<td>&gt; or = 1.75 nmol/mL/hr</td>
</tr>
<tr>
<td>Niemann-Pick</td>
<td>Sphingomyelinase</td>
<td>&gt; or = 2.5 nmol/mL/hr</td>
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<tr>
<td>Pompe</td>
<td>Acid Alpha-Glucosidase</td>
<td>&gt; or = 3.0 nmol/mL/hr</td>
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<tr>
<td>Krabbe</td>
<td>Galactocerebrosidase</td>
<td>&gt; or = 0.4 nmol/mL/hr</td>
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<tr>
<td>Fabry</td>
<td>Alpha-Galactosidase</td>
<td>&gt; or = 2.75 nmol/mL/hr</td>
</tr>
<tr>
<td>MPS I</td>
<td>Alpha-L-Iduronidase</td>
<td>&gt; or = 2.0 nmol/mL/hr</td>
</tr>
<tr>
<td>NA</td>
<td>C20 Lysophosphatidylcholine</td>
<td>&lt; or = 1.00 mcg/mL</td>
</tr>
<tr>
<td>NA</td>
<td>C22 Lysophosphatidylcholine</td>
<td>&lt; or = 0.25 mcg/mL</td>
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<tr>
<td>ALD/PBD/ALDH</td>
<td>C24 Lysophosphatidylcholine</td>
<td>&lt; or = 0.30 mcg/mL</td>
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<tr>
<td>ALD/PBD/ALDH</td>
<td>C26 Lysophosphatidylcholine</td>
<td>&lt; or = 0.30 mcg/mL</td>
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</tbody>
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**Lysosomal Storage Disorders Newborn Screen, Blood Spot**

**Clinical Information:** Lysosomes are intracellular organelles that contain hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease, which is inherited as an autosomal recessive lysosomal storage disorder, is caused by a deficiency of acid beta-glucosidase (glucocerebrosidase: GBA), resulting in increased storage of glucocerebroside (D-glucosylceramide). The deposition of glucocerebroside in macrophages of the reticuloendothelial system (Gaucher cells) causes organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease: -Type 1: adult/chronic -Type 2: acute neuropathic/infantile -Type 3: subacute neuropathic/juvenile Type 1, the most frequent form of the disease, is characterized by organomegaly, thrombocytopenia, and bone pain, and is frequent among the Ashkenazi Jewish population. Hepatosplenomegaly is usually present in all 3 types. Involvement of the central nervous system (CNS) is limited to the infantile type (type 2). Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and/or chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2. Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase, which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden
foam cells. Approximately 50% of cases have cherry-red spots in the macula. Niemann-Pick types A and B are caused by mutations in the SMPD1 gene. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, eventually, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. Because Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, in particular the juvenile and adult-onset forms, is often considered late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment by enzyme replacement therapy became available recently, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis.

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by mutations in the GALC gene resulting in a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Patients with this early infantile onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, has shown variable benefit. Fabry disease, caused by mutations in the GLA gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with <1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with >1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. MPS-I is caused by mutations in the IDUA gene and has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy.

**Useful For:** First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, MPSI, Niemann-Pick types A and B, and Pompe (Glycogen storage disorder type II)

**Interpretation:** An interpretive report is provided. When abnormal results are detected, a detailed
interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Medical Laboratories or elsewhere, and a phone number to reach 1 of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

Reference Values:
Not applicable

Clinical References:

Lysozyme (LYZ) Gene, Full Gene Analysis

Clinical Information: The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis, including those that encode transthyretin, apolipoprotein A1, apolipoprotein AII, fibrinogen alpha chain, gelsolin, cystatin C and lysozyme. Apolipoprotein A1, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Lysozyme (LYZ) gene-related familial visceral amyloidosis presents clinically with significant renal impairment. The renal dysfunction occurs at an early age and, in the absence of treatment, results in renal failure. Other manifestations of LYZ-related familial visceral amyloidosis include gastrointestinal involvement, cardiac disease, Sicca syndrome, and propensity towards petechiae, hemorrhage and hematoma, including hepatic hemorrhage. The bleeding tendency associated with LYZ-related familial visceral amyloidosis has included rupture of abdominal lymph nodes. Neupathoy is not a feature of LYZ-related familial visceral amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

Useful For: Confirming a diagnosis of lysozyme (LYZ) gene-related familial visceral amyloidosis

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:
Lysozyme (Muramidase), Plasma

**Clinical Information:** Lysozyme is a bacteriolytic enzyme that is found in some hematopoietic cells. It is primarily present in granulocytes, monocytes, and histiocytes. The enzyme is present in only minute amounts in lymphocytes; and is not present in myeloblasts, eosinophils, and basophils. Lysozyme in the plasma comes chiefly from the degradation of granulocytes and monocytes and its concentration reflects the turnover of these cells. Increases are seen in benign (eg, infection, inflammation) and malignant processes (eg, some leukemias). Plasma lysozyme is elevated in patients with acute or chronic granulocytic or monocytic leukemias and falls with successful treatment. Conversely, patients with lymphocytic leukemia may have depressed plasma lysozyme levels. Patients with renal disorders (including rejection of transplanted kidneys) or Crohn's disease (regional enteritis) also tend to have elevated levels of plasma lysozyme.

**Useful For:** Confirming marked increases in the granulocyte or monocyte pools as in granulocytic or monocytic leukemias, myeloproliferative disorders, and malignant histiocytosis Following the course of therapy in cases of chronic granulocytic or chronic monocytic leukemias

**Interpretation:** Levels >200 mcg/mL may be seen in acute nonlymphocytic leukemia (M2, M4, M5) or chronic granulocytic leukemias.

**Reference Values:**

> or =12 months: 2.7-9.4 mcg/mL

Reference values have not been established for patients who are <12 months of age.


Lysozyme, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0                    Negative
1  0.35-0.69          Equivocal
2  0.70-3.49          Positive
3  3.50-17.4          Positive
4  17.5-49.9          Strongly positive
5  50.0-99.9          Strongly positive
6  > or =100          Strongly positive Reference values apply to all ages.


FLYSO  58101  Lysozyme, Serum
Clinical Information:  Serum lysozyme levels may be elevated in acute myelomonocytic leukemia (FAB-M4), chronic myelomonocytic leukemia (CMML), and chronic myelocytic leukemia (CML). Increased serum lysozyme activity is present in tuberculosis, sarcoidosis, megaloblastic anemias, acute bacterial infections, ulcerative colitis, regional enteritis, and Crohn disease. Elevated serum lysozyme occurs during severe renal insufficiency, renal transplant rejection, urinary tract infections, pyelonephritis, glomerulonephritis, and nephrosis.
Reference Values:  0.00 - 2.75 ug/mL

FMCNE  57548  Macadamia Nut (Macadamia ternifolia) IgE
Interpretation:  Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.4 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 >100 Very High Positive
Reference Values:  <0.35 kU/L

MACE  82492  Mace, IgE
Clinical Information:  Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For:  Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Mackerel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Range</td>
<td>Interpretation</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
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<td></td>
</tr>
<tr>
<td>0.35-0.69</td>
<td>Equivocal</td>
<td></td>
</tr>
<tr>
<td>0.70-3.49</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>3.50-17.4</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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</tr>
<tr>
<td>50.0-99.9</td>
<td>Strongly positive</td>
<td></td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive</td>
<td></td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**MACR**

**Macroamylase**

**Reference Values:** Not Detected

**MCRPL**

**Macroprolactin, Serum**

**Clinical Information:** Prolactin is secreted by the anterior pituitary gland under negative control by dopamine, which is secreted by the hypothalamus. The only physiological function of prolactin is the stimulation of milk production. In normal individuals, the prolactin level rises in response to physiologic stimuli such as nipple stimulation, sleep, exercise, sexual intercourse, and hypoglycemia. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma), diseases of the hypothalamus, primary hypothyroidism, section compression of the pituitary stalk, chest wall lesions, renal failure, and ectopic tumors. Hyperprolactinemia may also be caused by the presence of a high-molecular-mass complex of prolactin called macroprolactin (typically due to prolactin bound to immunoglobulin). In this situation, the patient is asymptomatic. Hyperprolactinemia attributable to macroprolactin is a frequent cause of misdiagnosis and mismanagement of patients. Macroprolactin should be considered if, in the presence of elevated prolactin levels, signs and symptoms of hyperprolactinemia are absent, or pituitary imaging studies are not informative.

**Useful For:** Determining biologically active levels of prolactin, in asymptomatic patients with elevated prolactin levels Ruling out the presence of macroprolactin

**Interpretation:** When the percentage of the precipitated prolactin (complexed) fraction of total prolactin is <50%, the specimen is considered negative for macroprolactin. When total prolactin exceeds the upper reference limit and macroprolactin is negative, other causes for hyperprolactinemia should be explored. When the percentage of the precipitated (complexed) prolactin fraction of total prolactin is > or =50%, the specimen is considered positive for the presence of macroprolactin. Following macroprolactin precipitation, a patient whose unprecipitated prolactin level is greater than the upper limit of the total prolactin reference range may have hyperprolactinemia. See PRL/8690 Prolactin, Serum for interpretation of prolactin levels.

**Reference Values:**

**TOTAL PROLACTIN**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Males</td>
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</tr>
<tr>
<td>&lt; or =18 years: not established</td>
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</tr>
<tr>
<td>&gt;18 years: 4.0-15.2 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>&lt; or =18 years: not established</td>
<td></td>
</tr>
<tr>
<td>&gt;18 years: 4.8-23.3 ng/mL</td>
<td></td>
</tr>
</tbody>
</table>
Percent of the precipitated (complexed) prolactin fraction of the total prolactin <50% (considered negative for macroprolactin)

Unprecipitated prolactin levels are expected to be within the total prolactin reference range.


**Magnesium, 24 Hour, Urine**

**Clinical Information:** Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form, while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct. Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys' ability to excrete it, or a combination of the 2. Magnesium is an inhibitor of calcium crystal growth, and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

**Useful For:** Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk

**Interpretation:** Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium >24 mg/day or fractional excretion >0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

**Reference Values:**
51-269 mg/24 hr
Reference values have not been established for patients <18 years and >83 years of age. Reference values apply to 24-hour collections.


**Magnesium, Random, Urine**

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile, Pediatric, Random, Urine.
**Magnesium, Random, Urine**

**Clinical Information:** Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form, while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct. (1) Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys’ ability to excrete it, or a combination of the two. (2) Magnesium is an inhibitor of calcium crystal growth, and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

**Useful For:** Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk.

**Interpretation:** Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium >24 mg/day or fractional excretion >0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

**Reference Values:**
Random Magnesium/Creatinine Ratio: > or =0.035 mg/mg

Reference values have not been established for patients <18 years and >83 years of age.


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**Magnesium, Red Blood Cell**

**Reference Values:**
3.5 â€“ 7.1 mg/dL

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**Magnesium, Serum**

**Clinical Information:** Magnesium along with potassium is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate (ATP)-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The
serum magnesium level is kept constant within very narrow limits. Regulation takes place mainly via the kidneys, primarily via the ascending loop of Henle. Conditions that interfere with glomerular filtration result in retention of magnesium and hence elevation of serum concentrations. Hypermagnesemia is found in acute and chronic renal failure, magnesium overload, and magnesium release from the intracellular space. Mild-to-moderate hypermagnesemia may prolong atrioventricular conduction time. Magnesium toxicity may result in central nervous system (CNS) depression, cardiac arrest, and respiratory arrest. Numerous studies have shown a correlation between magnesium deficiency and changes in calcium-, potassium-, and phosphate-homeostasis which are associated with cardiac disorders such as ventricular arrhythmias that cannot be treated by conventional therapy, increased sensitivity to digoxin, coronary artery spasms, and sudden death. Additional concurrent symptoms include neuromuscular and neuropsychiatric disorders. Conditions that have been associated with hypomagnesemia include chronic alcoholism, childhood malnutrition, lactation, malabsorption, acute pancreatitis, hypothyroidism, chronic glomerulonephritis, aldosteronism, and prolonged intravenous feeding.

**Useful For:** Magnesium levels may be used to monitor preeclampsia patients being treated with magnesium sulfate, although in most cases monitoring clinical signs (respiratory rate and deep tendon reflexes) is adequate and blood magnesium levels are not required.

**Interpretation:** Symptoms of magnesium deficiency do not typically appear until levels are < or =1.0 mg/dL. Levels > or =9.0 mg/dL may be life-threatening.

**Reference Values:**
- 0-2 years: 1.6-2.7 mg/dL
- 3-5 years: 1.6-2.6 mg/dL
- 6-8 years: 1.6-2.5 mg/dL
- 9-11 years: 1.6-2.4 mg/dL
- 12-17 years: 1.6-2.3 mg/dL
- >17 years: 1.7-2.3 mg/dL


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**FMME**

**Mahi Mahi IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
- <0.35 kU/L

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**FMASC**

**Malaria Antibody Screen (P. falciparum, P. vivax, P. malariae, P. ovale), IFA**

**Reference Values:**
- Reference Range: Pos = > 1:64  Neg <1:64

- < 64 - Probably no recent clinical involvement with malaria
- => 64 - In U.S. citizens (brief exposure) may reflect recent infection; in some areas of the world, may be maximum titer demonstratable even in clinical cases.

In U.S. citizens with brief exposure to infection, a PLASMODIUM FALCIPARUM titer of =>1:64 may reflect recent infection. Speciation of the infecting malaria parasite is made by using four IFA slides prepared with P. FALCIPARUM, P. VIVAX, P. MALARIAE and P. OVALE, respectively. Antibody titers in U.S. citizens rarely persist more than six (6) months after chemotherapeutic cure. Titers in people with prolonged exposure and in people native to malaria endemic areas may persist for years because of...
relapses. Due to the increased volume of diagnostic specimens and to maximize the use of our malaria slides, we now titrate specimens at dilutions of 1:16 and 1:64. We will report immunofluorescence results that react at dilutions equal to or less than 1:16 as negative. Tests that react at dilutions of 1:64 will be reported as positive. By eliminating the reactivity of specimens at a dilution of 1:4 we are not changing the sensitivity of the immunofluorescence test.

**LMALP**

**Clinical Information:** Malaria is a major tropical disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. Ninety percent of the deaths occur in sub-Saharan Africa and most of these occur in children <5 years old; it is the leading cause of mortality in this age group. This disease is also widespread in Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers to and visitors from endemic areas. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a similar parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating Plasmodium falciparum and Plasmodium knowlesi from other species is important since both can cause life-threatening infections. In addition, Plasmodium falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and speciation of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform speciation by microscopy. Finally, Babesia parasites have a similar appearance to Plasmodium falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. PCR is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias, and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment.


**Interpretation:** A positive result indicates the presence of Plasmodium nucleic acid and melting curve analysis indicates the infecting species. When the malaria PCR is positive, the blood films will be examined so that the percentage of parasitemia can be calculated. The percentage of parasitemia will follow under reflex test ID PARCT.

**Reference Values:**

*Negative*

If positive, percent parasitemia will be calculated and reported.

**Clinical Information:** Malaria is a potentially life-threatening disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. It is widespread in sub-Saharan Africa, Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers and visitors from endemic areas. Examination of the thin film allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis. The degree of parasitemia may change rapidly due to natural parasite replication and administration of antimalarial therapies. Therefore, the percent parasitemia should be calculated upon initial diagnosis and then monitored over time with treatment.

**Useful For:** Only orderable as a reflex. For more information see LMALP / Malaria PCR with Parasitemia Reflex. Calculation of percent parasitemia that can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis.

**Interpretation:** The percentage parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalaria drugs.

**Reference Values:** Only orderable as a reflex. For more information see LMALP / Malaria PCR with Parasitemia Reflex. A percent parasitemia is provided following a positive result for Malaria PCR with Parasitemia Reflex.

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**Malaria, Molecular Detection, PCR Only**

**Clinical Information:** Malaria is a major tropical disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. Ninety percent of the deaths occur in sub-Saharan Africa and most of these occur in children <5 years old; it is the leading cause of mortality in this age group. This disease is also widespread in Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers to and visitors from endemic areas. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a similar parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating Plasmodium falciparum and Plasmodium knowlesi from other species is important since both can cause life-threatening infections. In addition, Plasmodium falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform species identification by microscopy. Finally, Babesia parasites have a similar appearance to Plasmodium falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. PCR is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias, and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment. This test does not include blood smear examination or calculation of parasitemia.

**Useful For:** Detection of Plasmodium DNA and identification of the infecting species. An adjunct to conventional microscopy of Giemsa-stained films, particularly in cases of low percent parasitemia or suboptimal parasite morphology. Detection and confirmatory identification of Plasmodium species: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi.
**Interpretation:** A positive result indicates the presence of Plasmodium nucleic acid and melting curve analysis indicates the infecting species.

**Reference Values:**
Negative


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**MAAN 82396**

**Maleic Anhydride, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**MALT 82834**

**Malt, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**MAML2 (11q21) Rearrangement, Mucoepidermoid Carcinoma (MEC), FISH, Tissue**

**Clinical Information:** Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland neoplasm, representing over 30% of all malignant salivary gland tumors. The diagnosis of MEC can be quite challenging due to the degree of histologic overlap with other glandular, clear cell, or oncocytic salivary gland tumors. MAML2 rearrangements are detectable in 80% to 85% of MEC, but not in morphologic mimics such as oncocytic cystadenoma, Warthin tumor, oncocytoma, oncocytic carcinoma, acinic cell carcinoma, and metastatic renal cell carcinoma.

**Useful For:** Supporting a diagnosis of mucoepidermoid carcinoma

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds
the normal cutoff for the MAML2 probe. A positive result is consistent with a diagnosis of mucoepidermoid carcinoma (MEC). A negative result suggests no rearrangement of the MAML2 gene region at 11q21. However, this result does not exclude the diagnosis of MEC.

**Reference Values:**
An interpretive report will be provided.


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**Mandarin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Manganese, 24 Hour, Urine

Clinical Information: Manganese (Mn) is an essential trace element with many industrial uses. Manganese is the 12th most abundant element in the earth's crust and is used predominantly in the production of steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly or not at all; neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthria, axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Few cases of manganese deficiency or toxicity due to ingestion have been documented. Only 1% to 3% manganese is absorbed via ingestion, while most of the remaining manganese is excreted in the feces. As listed in the United States National Agriculture Library, manganese adequate intake is 1.6 mg/day to 2.3 mg/day for adults. This level of intake is easily achieved, without supplementation, by a diverse diet including fruits and vegetables, which have higher amounts of manganese than other food types. Patients on a long-term parenteral nutrition should receive manganese supplementation and should be monitored to ensure that circulatory levels of manganese are appropriate.

Useful For: Monitoring manganese exposure Nutritional monitoring Clinical trials

Interpretation: Manganese in urine represents the excretion of excess manganese from the body. Elevated levels may indicate occupational exposure or excessive nutritional intake. Specimens from normal individuals have very low levels of manganese.

Reference Values:
<4.0 mcg/specimen
Reference values have not been established for patients that are <18 years of age.


Manganese, Blood

Clinical Information: Manganese (Mn) is a trace element that is an essential cofactor for several enzymes, including 1 form of superoxide dismutase and the gluconeogenic enzymes: pyruvate carboxylase and isocitrate dehydrogenase. It circulates in the serum as a metalloprotein complex with any of several proteins. The +2 and +3 states are of biological significance, but speciation in the analysis has not been studied sufficiently to determine its value. The required daily intake of 1 to 6 mg is readily supplied by a normal diet with a diverse mixture of fruits and vegetables. Manganese ores and alloys are refined and used in the making of batteries, welding rods, and high-temperature refractory materials. Environmental exposure occurs from inhalation and ingestion of manganese-containing dust and fumes occurring from the refinement processes. It is likely that inhaled Mn is mobilized up the trachea and swallowed; uptake through the gut is inefficient, about 10%. The major compartment for circulating Mn is the erythrocytes, bound to hemoglobin, with whole blood concentrations of Mn (in patients with normal levels) being 10 times that of the serum. Mn passes from the blood to the tissues quickly. Concentrations in the liver are highest, with 1 mg Mn/kg to 1.5 mg Mn/kg (wet weight) in normal individuals. The half-life of Mn in the body is about 40 days, with elimination primarily through the feces. Only small amounts are excreted in the urine. Environmental sources of Mn can lead to toxicity. The primary sites of
toxicity are the central nervous system (CNS) and the liver. Acute exposure to Mn fumes gives rise to symptoms common to many metal exposures including fever, dry mouth, and muscle pain. Chronic exposure of several months or more gives rise to CNS symptoms and rigidity, with increased scores on tremor testing and depression scales, as well as generalized parkinsonian features. Confined-space welders have been extensively studied because of their ongoing exposure to metal fumes, but the reported results are difficult to assign to any single metal as the origin of symptoms because of worksite variability, lack of adequate controls, and analytical issues.(1) Nevertheless, reports frequently describe significant increases in Mn levels in the whole blood (or erythrocytes) and in the CNS of these workers, with some evidence that circulating levels decrease following removal of individuals from sources of exposure. The mechanism of Mn-induced neurotoxicity is not clear. While Parkinson-like symptoms are found, the damage to nerve cells appears to be to the globus pallidus, while the nigrostriatal pathway (the focus of abnormality in Parkinson disease) is intact (although some claim it is dysfunctional). Increased levels of Mn in the CNS are not necessarily found in manganism, but this could be due to the use of inadequate analytical methodology. Animal studies, while plentiful and useful for pharmacokinetic modeling and possibly for studying mechanisms of hepatotoxicity, are of little value in extrapolation to CNS aberrations in humans because of species-to-species variability in absorption and distribution, and widely divergent psychological means of evaluation.(2) Elevated levels of whole blood Mn have been reported, with and without CNS symptoms, in patients with hepatitis B virus-induced liver cirrhosis, in patients on total parenteral nutrition (TPN) with Mn supplementation, and in infants born to mothers who were on TPN. The studies in cirrhotic patients with extrapyramidal symptoms indicate a possible correlation between whole blood Mn and that measured by T1-weighted magnetic resonance in the globus pallidus and midbrain, with whole blood Mn levels being 2-fold or more, higher than normal. Increases in whole blood Mn over time may be indicative of future CNS effects. The data on TPN patients is based on anecdotes or small studies and is highly variable, as is that obtained in infants.(3) Behcet disease, a form of chronic systemic vasculitis, has been reported to exhibit 4-fold increase in erythrocyte Mn and it is suggested that increased activity of superoxide dismutase may contribute to the pathogenesis of the disease. Mn has been reported as a contaminant in “garage” preparations of the abused drug methcathinone. Continued use of the drug gives rise to CNS toxicity typical of manganism.(4) Reports of suspected toxicity due to gustatory excess, even the drinking of large quantities of Mn-rich tea, may be dismissed as anecdotal and largely due to chance. For monitoring therapy, whether of environmental exposure, TPN, or cirrhosis, whole blood levels have been shown to correlate well with neuropsychological improvement, although whether the laboratory changes precede the CNS or merely track with them is unclear as yet. It is recommended that both CNS functional testing and laboratory evaluation be used to monitor therapy of these patients. Long-term monitoring of Behcet disease has not been reported, and it is not known if the Mn levels respond to therapy.

**Useful For:** Evaluation of central nervous system symptoms similar to Parkinson disease in manganese miners and processors Characterization of liver cirrhosis Therapeutic monitoring in treatment of cirrhosis, parenteral nutrition-related Mn toxicity and environmental exposure to Mn Evaluation of Behcet disease

**Interpretation:** Whole blood levels above the normal range are indicative of manganism. Values between 1 and 2 times the upper limit of normal may be due to differences in hematocrit and normal biological variation, and should be interpreted with caution before concluding that hypermanganesemia is contributing to the disease process. Values greater than twice the upper limit of normal correlate with disease. For longitudinal monitoring, sampling no more frequently than the half-life of the element (40 days) should be used.

**Reference Values:**

4.7-18.3 ng/mL

**Clinical References:**

Manganese, Red Blood Cell

**Reference Values:**
- Manganese, Plasma: <2.0 ng/mL
- Manganese, RBC: 11.0 - 23.0 ng/mL

Manganese is highly concentrated in the cellular elements of blood. Hemolysis of the cellular elements that is unobservable to the naked eye can result in elevated plasma manganese concentrations.

Manganese, Serum

**Clinical Information:** Manganese (Mn) is a trace essential element with many industrial uses. The twelfth most abundant element in the earth's crust, nearly all mined manganese is consumed in the production of ferromanganese, which is then used to remove oxygen and sulfur impurities from steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to progress through 3 stages. Levy describes these stages. “The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgement, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthrian axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled.”(1) Few cases of manganese deficiency or toxicity due to ingestion have been documented. Only 1% to 3% manganese is absorbed via ingestion, while most of the remaining manganese is excreted in the feces. As listed in the United States National Agriculture Library, manganese adequate intake is 1.6 mg/day to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of manganese than other food types. Patients on a long-term parenteral nutrition should receive manganese supplementation and should be monitored to ensure that circulating levels of manganese are appropriate.

**Useful For:** Monitoring manganese exposure Nutritional monitoring Clinical trials

**Interpretation:** Serum manganese results above the reference values suggest recent exposure.

**Reference Values:**
- <2.4 ng/mL

Reference values have not been established for patients that are <18 years of age.

**Clinical References:**

Manganese/Creatinine Ratio, Random, Urine

**Clinical Information:** Manganese (Mn) is an essential trace element with many industrial uses. Manganese is the 12th most abundant element in the earth's crust and is used predominantly in the production of steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly or not at all; neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to
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**Useful For:** Monitoring manganese exposure Nutritional monitoring Clinical trials

**Interpretation:** Manganese in urine represents the excretion of excess manganese from the body, and may be used to monitor exposure or excessive nutritional intake.

**Reference Values:**

<4.0 mcg/g creatinine

Reference values have not been established for patients that are <18 years of age.


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**Mango, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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2 0.70-3.49   Positive
3 3.50-17.4   Positive
4 17.5-49.9   Strongly positive
5 50.0-99.9   Strongly positive
6 > or =100   Strongly positive Reference values apply to all ages.


FMBL

Mannan Binding Lectin (MBL)

Reference Values:
>100 ng/mL

Investigators most frequently use 100 ng/mL as the threshold for defining an MBL deficiency. MBL values below this value may be associated with increased susceptibility to infection.

Mannose-Binding Lectin, Serum

Clinical Information: Mannose-binding lectin (MBL) is a member of the collectin family of proteins that are characterized structurally by the presence of collagenous regions and lectin domains in the same subunit. The subunit structure of MBL is comprised of three 32kDa peptide chains organized in a triple helix with 3 C-terminal lectin domains. Circulating (functional) MBL is comprised of oligomers of subunits (dimers through tetramers account for approximately 75% of circulating MBL) that are associated with an MBL-associated serine protease (MASP). There is a single MBL gene (4 exons) on chromosome 10 with 4 known allelic variants: wild type MBL (A), and 3 mutant forms B, C, and D caused by point mutations in 3 different codons. The mutant forms of MBL form oligomers poorly, and have diminished complement activating activity. Multimeric MBL binds to many different oligosaccharide moieties, including those in the cell walls of many different bacteria, yeasts, and some viruses, including HIV 1, HIV 2, and influenza A. Binding of MBL results in complement activation by the classical pathway through activation of complement 4 (C4) by MASP, and surface bound MBL enhances phagocytosis by interacting with collectin receptors on phagocytic cells. Mutations of MBL codons (homozygous or heterozygous haplotypes) are associated with diminished opsonophagocytic activity and diminished serum levels of MBL measured immunochemically (MBL deficiency). MBL-deficient individuals have increased susceptibility to infection particularly if MBL deficiency occurs concomitantly with another heritable immune system abnormality, eg, C4 null alleles or immunoglobulin class or subclass deficiencies.

Useful For: Evaluation of children and adults with a clinical history of recurrent infections Results may be useful for genetic counseling and support aggressive management of recurrent infections in patients with reduced levels of mannose-binding lectin

Interpretation: Diminished levels of serum mannose-binding lectin (MBL) are consistent with the diagnosis of MBL deficiency. Levels <7.8 ng/mL are associated with homozygous or mixed heterozygous mutant forms of MBL or mutations in the MBL promoter gene.

Reference Values:
> or =7.8 ng/mL
This reference range applies only to adults.
See Cautions for further information regarding the reference range and clinical interpretation.
**Clinical References:**

**Maple Red (Acer rubrum) IgE**

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.35 Below Detection 1 0.35–0.69 Low Positive
2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive
4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive
6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**MAPT Gene, Sequence Analysis, 7 Exon Screening Panel**

**Clinical Information:**
Frontotemporal dementia is a familial adult-onset, presenile dementia that affects the frontal and temporal cerebral cortices. Clinical presentation is variable and includes changes in behavior, difficulties with language, rigidity, palsy, and saccadic (rapid) eye movement. Symptoms generally begin between 40 and 60 years of age, with mean age of onset at approximately 45 years, and typically last between 5 and 10 years, progressing to severe dementia and mutism. The presentation of frontotemporal dementia may be confused with other dementias, including Alzheimer disease. It is important to distinguish between these different dementias because progression and patient management are different for the various dementias. Based on the immunohistochemical staining, there are 2 main subtypes of frontotemporal lobular degeneration (FTLD): tau-positive FTLD and tau-negative FTLD with ubiquitin-positive inclusions (FTLD-U). Mutations in the MAPT gene have been identified in patients with tau-positive FTLD; mutations in the progranulin gene (GRN) have been identified in patients with FTLD-U. Both MAPT and GRN are located on chromosome 17q21. The MAPT gene encodes the microtubule-associated tau protein. A number of mutations have been identified in the MAPT gene that result in aggregation of the tau protein. Although there is variable expression of disease presentation and severity within and between families, the hallmark neurologic lesion constitutes tau-positive protein inclusion bodies. Most clinically significant mutations are found in exons 9 through 13. Several intronic mutations, associated with alternative splicing of the mRNA, contribute to the variability of expression of the disease traits. Mutations in the MAPT gene have also been identified in cases of progressive supranuclear palsy, corticobasal degeneration, and dementia with epilepsy.

**Useful For:**
Aiding in the diagnosis of frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, and dementia with epilepsy
Distinguishing the diagnosis of frontotemporal dementia from other dementias, including Alzheimer disease
Identifying individuals who are at risk of frontotemporal dementia

**Interpretation:**
All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. All variants will be reported in reference to transcript NM_001123066 (build GRCh37 (hg19)).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
MARE

Mare's Milk, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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MFRGP

Marfan Syndrome and Related Disorders Multi-Gene Panel, Blood

Clinical Information: Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and mitral valve prolapse and aortic root
dilatation/dissection are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of FBN1. Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the FBN1 gene include autosomal dominant ectopia lenti (displacement of the lens of the eye), thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis).

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities, and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants of the SMAD3 gene have been reported in families with a LDS-like phenotype and tortuosity and early onset osteoarthritis. TAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is ACTA2, followed by TGFBR1 and TGFBR2, and MYH11. Variants in the MYLK gene have been reported in a small subset of families with familial TAAD. TGF2 variants have also been reported in families with TAAD and systemic features that overlap with LDS and MFS. The COL3A1 gene causes Ehlers Danlos syndrome type IV (vascular type), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously. Autosomal dominant variants of the FBN2 gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm. Variants of the CBS gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting. Mutations in the SKI gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS, but, when present, it can be severe. Homozygous and compound heterozygous loss of function variants in the SLC2A10 gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features. Genes included in Marfan Syndrome and Related Disorders Multi-Gene Panel: Gene Protein Inheritance Known Association ACTA2 Actin, alpha-2, smooth muscle, aorta AD TAAD CBS Cystathionine beta-synthase AR Homocystinuria COL3A1 Collagen, type III, alpha-1 AD Ehlers-Danlos syndrome Type IV (vascular type) FBN1 Fibrillin 1 AD Marfan syndrome/TAAD/Ectopia Lentis/ MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome FBN2 Fibrillin 2 AD Congenital Contractural Arachnodactyly MYH11 Myosin, heavy chain 11, smooth muscle AD TAAD MYLK Myosin light chain kinase AD TAAD SKI V-SKI avian sarcoma viral oncogene homolog AD Shprintzen-Goldberg syndrome SLC2A10 Solute carrier family 2 (facilitated glucose transporter), member 10 AR Arterial Tortuosity syndrome/TAAD (Autosomal Recessive) SMAD3 Mothers against decapentaplegic, drosophila, homolog of, 3 AD Loeys-Dietz syndrome/TAAD TGFBR2 Transforming growth factor, beta-2 AD TAAD TGFBR1 Transforming growth factor-beta receptor, type I AD Loeys-Dietz syndrome/TAAD TGFBR2 Transforming growth factor-beta receptor, type II AD Loeys-Dietz syndrome/TAAD Abbreviations:

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder Second-tier testing for patients in whom previous targeted gene variant analyses for
specific Marfan and related genes were negative. Establishing a diagnosis of a Marfan or a related disorder in some cases, allowing for appropriate management and surveillance for aneurysms and other disease features based on the gene involved. Identifying variants within genes known to be associated with increased risk for aneurysms and other disease features allowing for predictive testing of at-risk family members.

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Marjoram, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**MASN**

**26470**

**Masson's Trichrome, Nrv ST**

**Reference Values:**

Report sent under separate cover

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**MATCC**

**35479**

**Maternal Cell Contamination, Molecular Analysis**

**Clinical Information:** One of the risks associated with prenatal testing is maternal cell contamination (MCC), which can occur when a fetal specimen comes into contact with maternal blood or tissue. The risk of MCC is associated with procedures such as chorionic villus sampling, amniocentesis, or extraction of fetal blood from the umbilical cord (cord blood). If MCC is present, the maternal DNA may mask the results of any genetic testing performed on the fetal DNA. Therefore, the results of prenatal testing may be compromised. To rule out the presence of MCC, a maternal blood specimen is necessary for comparison of maternal and fetal chromosomal markers. The presence of both maternal and nonmaternal alleles for each fetal marker indicates the fetal specimen is not contaminated. MCC is confirmed when both alleles in the fetus are maternal.

**Useful For:** Ruling out the presence of maternal cell contamination within a fetal specimen This test is required for all prenatal testing performed in Mayo's molecular and biochemical genetics laboratories

**Interpretation:** An interpretive report will be provided.

**Reference Values:**

An interpretative report will be provided.
Maternal Serum Screening, Integrated, Specimen #1

Clinical Information: This test combines a first- and second-trimester specimen to screen low-risk pregnancies for Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). Collection of two blood samples is required for this test. A first trimester ultrasound to measure the fetal nuchal translucency (NT) is optional (see special instructions). Patient demographics and analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks of ONTD, DS and T18. Markers used for assessment of risk include first-trimester PAPP-A with or without NT and second-trimester AFP, hCG, unconjugated estriol (uE3) and dimeric Inhibin A. A DS risk of 1 in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 87 percent at a screen positive rate of 1.0%. A T18 risk of 1 in 100 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 90 percent at a screen positive rate of <0.5%. ARUP uses a singleton AFP MoM cut off of >or= 2.5. If the interpretation is "high AFP," there is an increased risk of an ONTD in the pregnancy. This cutoff value predicts a detection rate of 80% at a screen positive rate of 1.5%. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age. Pregnancies at an increased risk for ONTD with an AFP MoM <2.5, but a risk of 1 in 250 or worse, are also reported as abnormal. This is usually due to a family history of ONTD, the use of certain seizure medications by the patient during pregnancy, or the presence of maternal insulin-dependent diabetes, any of which increases a patients risk for ONTD. An increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome (uE3 <or= 0.14 MoM) and poor fetal outcome (hCG >or= 3.5 MoM) is reported as "see note".

Useful For: Helpful to identify pregnancies at increased risk of having a child with Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). This test is not diagnostic.

Interpretation: The first specimen of an integrated Maternal Serum Screening is used to measure PAPP-A. A second sample must be submitted for a final interpretive report. Acceptable date ranges to draw the second samples will be provided in the Integrated-1 report.

Reference Values: An interpretive report will be provided.

Part 2 must be completed in order to receive an interpretable result.

If the second specimen is not received for sequential screening, the results are uninterpretable and no maternal risk will be provided.

Maternal Serum Screening, Integrated, Specimen #2

Clinical Information: This test combines a first-and second-trimester specimen to screen low-risk pregnancies for Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). Collection of two blood samples is required for this test. A first trimester ultrasound to measure the fetal nuchal translucency (NT) is optional (see special instructions). Patient demographics and analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks for ONTD, DS and T18. Markers used for assessment of risk include first-trimester PAPP-A with or without NT and second-trimester AFP, hCG, unconjugated estriol (uE3), and dimeric Inhibin A. A DS risk of 1 in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 87 percent at a screen positive rate of 1.0%. A T18 risk of 1 in 100 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 90 percent at a screen positive rate of <0.5%. ARUP uses a singleton AFP MoM cutoff of >or=2.5. If the interpretation is "high AFP," there is an increased risk of an ONTD in the pregnancy. This cutoff value predicts a detection rate of 80% at a screen positive rate of 1.5%. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age. Pregnancies at an increased risk for ONTD with an AFP MoM <2.5, but a risk of 1 in 250 or worse, are also reported as abnormal. This is usually due to a family history of ONTD, the use of certain seizure medications by the patient during pregnancy, or the presence of maternal insulin-dependent diabetes, any of which increases a patient's priori risk for ONTD. An increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome (uE3 <or=0.14 MoM) and poor fetal outcome (hCG >or=3.5 MoM) is
Useful For: Helpful to identify pregnancies at increased risk of having a child with Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). This test is not diagnostic.

Interpretation: An interpretive report will be provided. See clinical informations sections. Part 2 must be completed in order to receive an interpretable result. If the second specimen is not received for sequential screening, the results are uninterpretable and no maternal risk will be provided.

Reference Values: An interpretive report will be provided.

Mayo Stratification for Myeloma and Risk-Adapted Therapy Report

Clinical Information: Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. The Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) algorithm classifies patients into either standard or high-risk categories based on the results of 3 assays: the plasma cell proliferation result, conventional chromosome analysis, and FISH for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with multiple myeloma, which can assist in determining treatment and management decisions Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: An interpretive report is provided. Patients are classified as high risk, intermediate, or standard risk.

Reference Values: PCPRO
Estimated S-phase of >1.5% associated with more aggressive disease

CHROMOSOMES, mSMART EVALUATION
An interpretative report will be provided.

PLASMA CELL PROLIF, cIg, FISH
An interpretative report will be provided.

Liposarcoma/Atypical Lipomatous Tumor, FISH, Tissue

Clinical Information: The histological discrimination of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT) from lipoma can be diagnostically challenging. However, standard cytogenetic identification of ring and giant rod chromosomes strongly support the diagnosis of WDL/ALT. These abnormal chromosomes are mainly composed of amplified sequences derived from chromosome bands 12q13-15, and contain several amplified genes including MDM2, CPM, CDK4, and TSPAN31. MDM2 is amplified in >99% of WDL, and up to 30% of other types of sarcomas.

Useful For: Supporting a diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the MDM2 FISH probe (positive result). A positive result is consistent with amplification of the MDM2 gene locus (12q15) and supports the diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT). A negative result is consistent with absence of amplification of the MDM2 gene locus (12q15). However, negative results do not exclude the diagnosis of WDL/ALT. Amplification varies in individual tumors and among different cells in the same tumor.

Reference Values:
An interpretive report will be provided.


Meadow Fescue, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Meadow Foxtail, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive Reference values apply to all ages.</td>
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**Measles (Rubeola) Antibodies, IgG, Serum**

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is one of the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours. Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement. Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to <0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs. The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals.

**Useful For:** Determination of immune status of individuals to the measles virus Documentation of previous infection with measles virus in an individual without a previous record of immunization to measles virus

**Interpretation:** Positive: Antibody index (AI) value > or =1.1 The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies indicates prior exposure to the measles virus through infection or immunization. Individuals testing positive are considered immune to measles infection. Equivocal: AI value 0.9-1.0 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value < or =0.8 The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus.

**Reference Values:**
- Vaccinated: positive (> or =1.1 AI)
- Unvaccinated: negative (< or =0.8 AI)

**Clinical References:**

**Measles (Rubeola) Antibodies, IgM, Serum**

**Clinical Information:** Measles (rubeola) virus is a member of the family paramyxoviridae, which also includes mumps, respiratory syncytial virus, and parainfluenza viruses. Clinical infection with measles virus is characterized by a prodromal phase of high fever, cough, coryza, conjunctivitis, malaise, and Koplik's spots on the buccal mucosa. An erythematous rash then develops behind the ears and over the forehead, spreading to the trunk. Measles virus is highly contagious; pregnant women, immunocompromised, and nutritionally deficient individuals are at particularly high risk for serious complications of pneumonia and central nervous system involvement. Since intensive immunization
began in the United States more than 2 decades ago, the incidence of measles infection has been reduced from approximately 1/2 million cases annually in the 1960s to fewer than 500 cases in recent years. Atypical measles can occur in patients who received killed measles virus vaccine and subsequently have been infected with the wild type strain of the virus. In addition, many individuals remain susceptible to measles virus because of vaccine failure or nonimmunization. Screening for antibody to measles virus will aid in identifying these nonimmune individuals.

**Useful For:** Determining acute-phase infection with rubeola (measles) virus As an aid in identifying nonimmune individuals

**Interpretation:** Positive IgM results, with or without positive IgG results, indicate a recent infection with measles virus. Positive IgG results coupled with a negative IgM result indicate previous exposure to measles virus and immunity to this viral infection. Negative IgG and IgM results indicate the absence of prior exposure to rubeola and nonimmunity. Equivocal results should be followed up with a new serum specimen within 10 to 14 days.

**Reference Values:**
Negative (reported as negative or positive)

**Clinical References:**
1. Liebert UG: Measles virus infections of the central nervous system. Intervirology 1997;40:176-184

**Measles (Rubeola) Virus Antibody, IgM and IgG (Separate Determinations), Serum**

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours. Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement. Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to <0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs. The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection, but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals.

**Useful For:** Laboratory diagnosis of measles virus infection Determination of immune status of individuals to the measles virus Documentation of previous infection with measles virus in an individual without a previous record of immunization to measles virus
**Interpretation:** The presence of IgM-class antibodies, with or without the presence of IgG-class antibodies to measles virus may support a clinical diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase infection with measles virus. However serology may be negative for IgM-class antibodies in early disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class antibodies to measles should be limited to patients with clinically compatible disease. The presence of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the measles virus through infection or immunization. These individuals are considered immune to measles infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus. These individuals are considered nonimmune to measles virus infection.

**Reference Values:**

**IgM**
- Negative (reported as negative or positive)

**IgG**
- Vaccinated: positive (> or =1.1 AI)
- Unvaccinated: negative (< or =0.8 AI)

**Clinical References:**

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**FMECM 57760**

**Meconium Methadone Screen**

**Reference Values:**
The specimen was screened by Immunoassay at the following threshold concentrations:
- Methadone: 50 ng/gm

Positive results are confirmed by Chromatography with Mass Spectrometry (GC/MS) to limit of detection.

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**MECPZ 35484**

**MECP2 Gene, Full Gene Analysis**

**Clinical Information:** Methyl-CpG-binding protein 2 (MeCP2) is a transcriptional repressor protein encoded by the MECP2 gene located on the X chromosome. Genetic mutations in MECP2 alter the expression of targeted genes and can be associated with variable phenotypes in females including classic Rett syndrome, variant or atypical Rett syndrome, mild mental retardation, and asymptomatic carriers. Males with MECP2 mutations can present with variable phenotypes as well. The variability in males can, in part, be attributed to the type of MECP2 mutation present; point mutations are typically associated with severe neonatal encephalopathy and gene duplications are associated with MECP2 duplication syndrome. Full MECP2 gene analysis via sequencing and large duplication/deletion studies has been useful in identifying germline mutations in individuals with these clinical presentations. Rett Syndrome: Rett syndrome is an X-linked, panethnic condition with an incidence of approximately 1 in 8,500 to 1 in 15,000 females. Disease course typically begins after 6 to 18 months of apparently normal development with rapid regression in language and motor skills. A hallmark feature of this condition is repetitive, stereotyped hand movements, sometimes described as hand-wringing. Clinical criteria have been established for diagnosis of classic and atypical or variant Rett syndrome. Greater than 88% of females with a clinical diagnosis of classic Rett syndrome demonstrate a mutation by this test. The detection rate is approximately 43% for females with a clinical diagnosis of atypical or variant Rett syndrome. For
individuals in whom there is clinical suspicion for Rett syndrome, but clinical criteria are not met, the
detection rate is lower given the phenotypic overlap with other conditions (eg, Angelman syndrome).
Nonrandom X chromosome inactivation, resulting in phenotypic variability within families, has been
reported in females with MECP2 mutations. Although 99.5% of mutations associated with Rett syndrome
are de novo, asymptomatic or very mildly affected carrier mothers of classically affected daughters have
been reported. Genetic counseling should be provided with this, and the possibility of germline or somatic
mosaicism, in mind. MECP2 Duplication Syndrome: Although MECP2 mutations are reported in males,
these males typically do not present with classic Rett syndrome unless an abnormal karyotype (ie,
47,XXY) or somatic mosaicism is also present. More commonly, MECP2 mutations have been reported
in karyotypically normal males presenting with neonatal encephalopathy and mental retardation
syndromes. MECP2 duplication syndrome is an increasingly reported severe mental retardation syndrome
characterized by infantile hypotonia, absence of speech, and progressive spasticity. Seizures and recurrent
respiratory infections are commonly reported as well. These MECP2 gene duplications vary in size from
0.3 to 2.3 Mb. Although chromosome analysis can identify some larger duplications, other methods such
as multiplex ligation-dependent probe amplification (MLPA) can identify essentially all MECP2 gene
duplications. Males with nongene-duplication type mutations can present with other mental retardation
syndromes (ie, Angelman-like syndrome) or neonatal encephalopathy and early death. To date, all males
found to have an MECP2 duplication are clinically affected and have inherited the duplication from their
asymptomatic mothers. Therefore, mothers of sons with MECP2 duplication syndrome are thought to be
obligate carriers whose male offspring have a 50% risk of being affected.

Useful For: Diagnosis of Rett syndrome or other MECP2-related disorders

Interpretation: All detected alterations are evaluated according to American College of Medical
Genetics recommendations.(1) Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Van Esch H, Bauters M, Ignatius J, et al: Duplication of the MECP2 region is a frequent cause of severe
5. Hagberg B, Hanefeld F, Percy A, Skjedal O: An update on clinically applicable diagnostic criteria in
Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European
Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001 Eur J Paediatr Neurol

Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency
Full Gene Analysis

Clinical Information: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an autosomal
recessive inherited defect in the mitochondrial oxidation of fatty acids. The mitochondrial beta-oxidation
pathway plays a major role in energy production, especially during periods of fasting and physical
exertion. MCAD deficiency is prevalent among individuals of northern European origin, affecting 1 in
4,900 to 1 in 17,000 individuals, with a carrier frequency estimated as high as 1 in 40 for some
populations. Phenotypic expression of MCAD deficiency is episodic in nature (ie, asymptomatic between
attacks). Symptoms are typically precipitated by any stress (eg, fever, infection, vaccination) and mostly
occur during the first 2 years of life, although some cases have been diagnosed in adulthood.
Characteristic features of MCAD deficiency include: Reye-like syndrome (an acquired encephalopathy
characterized by recurrent vomiting, agitation, and lethargy), fasting intolerance with vomiting, recurrent
episodes of hypoglycemic coma, hypoketotic dicarboxylic aciduria, low plasma and tissue levels of

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carnitine, hepatic failure with fat infiltration (fatty liver), encephalopathy, and rapidly progressive
deterioration leading to death. MCAD deficiency has also been associated with sudden infant death or
sudden unexpected death syndrome. Review of clinical features and biochemical analysis via plasma
acylcarnitines (ACRN / Acylcarnitines, Quantitative, Plasma), fatty acid profile (FAO / Fatty Acid
Oxidation Probe Assay, Fibroblast Culture), urine organic acids (OAU / Organic Acids Screen, Urine),
and urine acylglycines (ACYLG / Acylglycines, Quantitative, Urine) are always recommended as the
initial evaluation for MCAD. If previously performed, the results of these biochemical assays should be
included with the specimen as they are necessary for accurate interpretation of the MCAD sequence
analysis. The MCAD gene (ACADM) maps to 1p31 and has 12 exons, spanning 44 kb of DNA. Most
mutations are family-specific with the exception of the recurrent A->G transition at nucleotide 985
(985A->G). Among MCAD-deficient patients, approximately 52% are homozygous for the 985A->G
mutation. The majority of the remaining patients are compound heterozygous for the 985A->G mutation
and a different mutation.

**Useful For:** Confirmation of diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
(as a follow-up to biochemical analyses) Screening of at-risk carriers of MCAD deficiency when an
affected relative has not had molecular testing Diagnosis of MCAD deficiency in autopsy specimens

**Interpretation:** All detected alterations are evaluated according to American College of Medical
Genetics recommendations.(1) Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
neonatal screening shows high incidence and unexpected mutation frequency. Pediatr Res 1995
May;37(5):675-678 3. Roe CR, Coates PM: Mitochondrial fatty acid oxidation. In The Metabolic and

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**Medulloblastoma, FISH, Tissue**

**Clinical Information:** Medulloblastoma is the most common malignant brain tumor in children.
Current treatment decisions are based on clinical variables. Biomarkers have been identified that allow
classification of medulloblastoma into subtypes that are associated with a specific clinical behavior. FISH
analyses for the MYCN, MYB, and MYC loci may be useful in medulloblastoma patients to help provide
prognostic information and guide treatment.

**Useful For:** Identifying MYCN amplification, MYC amplification, and monosomy of chromosome 6
(detected using MYB probe), to aid in the classification of medulloblastoma patients into specific clinical
categories

**Interpretation:** MYCN: -The MYCN locus is reported as amplified when the MYCN:D2Z1 ratio is
2.0 or greater and demonstrates 8 or more copies of the MYCN locus. -A tumor with a MYCN:D2Z1 ratio
<2.0 or demonstrating a ratio of 2.0 or greater with <8 copies of MYCN, is considered to lack
amplification of the MYCN locus. MYB: Monosomy of chromosome 6 is reported when the percent of
cells with the abnormality exceeds the normal cutoff for the probe set. MYC: -The MYC locus is reported
as amplified when the MYC:D8Z2 ratio is 2.0 or greater and demonstrates 8 or more copies of the MYC
locus. -A tumor with a MYC:D8Z2 ratio <2.0 or demonstrating a ratio of 2.0 or greater with <8 copies of
MYC, is considered to lack amplification of the MYC locus.

**Reference Values:**
An interpretive report will be provided.
**MEFVZ**

**MEFV Gene, Full Gene Analysis**

**Clinical Information:** Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory disease which is most prevalent in Mediterranean populations (Turks, Armenians, Sephardic Jews, Arabs), where the incidence is approximately 1 in 400 to 1 in 1000. FMF has been reported in other populations as well. FMF is characterized by recurrent febrile episodes with associated abdominal pain, pleuritis, arthritis, and, rarely, pericarditis and meningoiritis. Attacks typically occur 1 to 2 times per month and last 1 to 3 days. Age of onset is typically before 10 years. Amyloid A (AA) type amyloidosis is a severe complication of FMF which can lead to renal failure. Clinical features vary and some individuals with FMF present with amyloidosis as the first clinical manifestation of disease (classified as FMF type 2). FMF is caused by mutations in the MEFV gene encoding pyrin. FMF is typically inherited in an autosomal recessive fashion, but heterozygous mutation carriers may also develop symptoms. Ongoing prophylactic treatment with colchicine has been shown to reduce frequency and severity of febrile attacks and inhibit development of amyloidosis in the majority of patients with FMF. In particular, patients with 1 or 2 copies of the M694V mutation are typically responsive to colchicine treatment.

**Useful For:** Confirmation of familial Mediterranean fever (FMF) for patients with clinical features

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MEGR**

**Megrim, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Melaleuca leucadendron, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
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<tr>
<th>Class</th>
<th>IgE kU/L</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT

Melanoma Targeted Gene Panel by Next Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. MELP / Melanoma Targeted Gene Panel by Next Generation Sequencing, Tumor is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the following genes known to be associated with melanoma: BRAF, GNA11, GNAQ, KIT, and NRAS. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with melanoma. See Targeted Gene Regions Interrogated by Solid Tumor Targeted Cancer Gene Panel by Next Generation Sequencing in Special Instructions for details regarding the targeted gene regions identified by this test.

Useful For: Diagnosis and management of patients with melanoma

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretative report will be provided.

Melanoma, FISH, Tissue

Clinical Information: Melanocytic tumors arising in the skin can present a significant diagnostic challenge. While many lesions can be easily classified as benign nevi or malignant melanoma based on histologic features alone, there is a significant subset of lesions that cannot be clearly defined as either benign or malignant. Because the course of treatment for malignant melanoma relative to benign lesions varies significantly from the time of diagnosis, accuracy, and expediency of the diagnosis are of paramount importance. A FISH-based test panel has been developed that can be used as a diagnostic aid in the differentiation of malignant from benign melanocytic lesions. This test is intended to be used in conjunction with clinical and pathologic information to aid the pathologist in the differentiation of benign from malignant melanocytic lesions.

Useful For: An aid in the differentiation of benign from malignant melanocytic lesions when used in conjunction with clinical and pathologic information

Interpretation: The panel test is considered abnormal if certain parameters are met that have been shown to be observed in malignant melanocytic lesions and within normal limits if these parameters are not met. An abnormal result is not diagnostic of malignancy, nor does a normal result exclude malignancy. The results are intended to be interpreted in the context of the pathologic and clinical findings.

Reference Values:
An interpretive report will be provided.

Clinical References:

Melatonin

Reference Values:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9 years</td>
<td>Not Established</td>
</tr>
<tr>
<td>10-20 years</td>
<td>31.3-175.4 pg/mL</td>
</tr>
<tr>
<td>21-65 years</td>
<td>11.0-135.4 pg/mL</td>
</tr>
<tr>
<td>≥66 years</td>
<td>11.0-34.4 pg/mL</td>
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800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1288
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Melons, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td></td>
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</tr>
</tbody>
</table>

Meperidine (Demerol) and Normeperidine, serum

Clinical Information: Category: Narcotic Analgesic

Reference Values:
Meperidine:
Reference Range: 400 - 700 ng/ml

Normeperidine: No reference range provided

Mephedrone, MDPV and Methylone, Urine

Reference Values:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Units</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mephedrone</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>MDPV</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Methylone</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Qualitative analysis for Mephedrone, Methylenedioxyprovalerone (MDPV) and Methylone Screening threshold: 1.0 ng/mL

Mephobarbital and Phenobarbital, Serum

Clinical Information: Mephobarbital is an orally administered, methylated barbiturate used for the treatment of epilepsy.(1,2) It is demethylated by hepatic microsomal enzymes to generate its major metabolite, phenobarbital. During long-term use, most of mephobarbital's activity can be attributed to the accumulation of phenobarbital. Consequently, mephobarbital's pharmacological properties, toxicity, and clinical uses are the same as phenobarbital's.(1,2) The use of mephobarbital is uncommon as it offers no significant advantage over phenobarbital alone.(1,2)

Useful For: Monitoring of mephobarbital and phenobarbital therapy

Interpretation: The therapeutic range for mephobarbital is 1.0 to 7.0 mcg/mL. In children, the therapeutic range for phenobarbital is 15.0 to 30.0 mcg/mL; in adults the therapeutic range is 20.0 to 40.0 mcg/mL.

Reference Values:
M Ephobarbital
Therapeutic range: 1.0-7.0 mcg/mL
Toxic concentration: > or =15.0 mcg/mL

Phenobarbital
Therapeutic range
Children: 15.0-30.0 mcg/mL
Adults: 20.0-40.0 mcg/mL
Toxic concentration: > or =60.0 mcg/mL
Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.


Mercaptopurine (6-MP, Purinethol)
Reference Values:
Units: ng/mL

Mercaptopurine may be administered as an antineoplastic or may be present as a metabolite of the immunosuppressant drug azathioprine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses of either mercaptopurine or azathioprine produce 6-mercaptopurine serum concentrations of less than 1000 ng/mL.

**Mercury for Occupational Monitoring, Urine**

Clinical Information: Mercury (Hg), a well-known toxin, is essentially nontoxic in its elemental form. However, once it is chemically modified to the ionized, inorganic species, Hg(++) , it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH[3]Hg[+]), yields a species of Hg that is highly selective for lipid-rich tissue, such as the myelin sheath, and is very toxic. Industrial exposure is a major source of Hg intoxication.

Useful For: Screening potentially exposed workers for mercury toxicity in settings where a 24-hour collection is problematic

Interpretation: Urinary mercury (Hg) is the most reliable way to assess exposure to inorganic Hg, but the correlation between the levels of excretion in the urine and clinical symptoms is poor. The reference interval corresponds to the Occupational Safety and Health Administration (OSHA) guideline for Hg exposure. The ordering physician will be contacted regarding any result exceeding OSHA thresholds to determine the level of workplace exposure and follow-up action.

Reference Values:
MERCURY/CREATININE
<35 mcg/g


**Mercury, 24 Hour, Urine**

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity

Interpretation: Daily urine excretion of mercury >50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:
0-15 years: not established
> or =16 years: 0-9 mcg/specimen
Toxic concentration: >50 mcg/specimen

The concentration at which toxicity is expressed is widely variable between patients. 50 mcg/specimen is the lowest concentration at which toxicity is usually apparent.

Mercury, Blood

Clinical Information: Mercury (Hg) is essentially nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(+2), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH[3]Hg[+]), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Not Toxic - Hg(0) < Hg(+2) << CH(3)Hg(+) -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents such as chlorine. Hg(0) can be bioconverted to both Hg(+2) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(+2), CH(3)Hg(+), and (CH[3])(+2)Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(+2) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein-a stereoisomeric change-with subsequent loss of the unique activity associated with that protein. Because Hg(+2) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as CH(3)Hg(+), are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial flora present in the mouth converts a fraction of this to Hg(+2) and CH(3)Hg(+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain <0.3 mcg/g of mercury, but some game fish contain >2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is <50 mcg/day.

Useful For: Detecting mercury toxicity

Interpretation: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually <10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is >50 ng/mL if exposure is due to alkyl Hg, or >200 ng/mL if exposure is due to Hg(+2).

Reference Values:
Normal: 0-9 ng/mL
Reference values apply to all ages.

including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If the hair can be segregated by length, such an exercise can be useful in identifying the time of exposure.

**Useful For:** Detecting mercury exposure

**Interpretation:** Normally, hair contains <1 mcg/g mercury; any amount more than this indicates that exposure to more than normal amounts of mercury has occurred.

**Reference Values:**
- 0-15 years: not established
- > or =16 years: 0.0-0.9 mcg/g of hair


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**Mercury, Nails**

**Clinical Information:** Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms. If the nails can be segregated by length, such an exercise can be useful in identifying the time of exposure.

**Useful For:** Detecting mercury exposure

**Interpretation:** Normally, nails contains <1 mcg/g mercury; any amount more than this indicates that exposure to more than normal amounts of mercury has occurred.

**Reference Values:**
- 0-15 years: not established
- > or =16 years: 0.0-0.9 mcg/g of nails


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**Mercury, Random, Urine**

**Clinical Information:** The correlation between the levels of excretion in the urine and the clinical symptoms is considered poor, but urinary mercury (Hg) is the most reliable way to assess exposure to inorganic mercury. For additional information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity

**Interpretation:** Daily urine excretion >50 mcg/day indicates significant exposure (per World Health Organization standard).

**Reference Values:**
- 0-15 years: not established
- > or =16 years: 0-9 mcg/L

**Mesenchymal Chondrosarcoma, by Reverse Transcriptase PCR (RT-PCR)**

**Clinical Information:** Mesenchymal chondrosarcoma is a rare sarcoma of bone and soft tissues. The histological diagnosis of mesenchymal chondrosarcoma can be challenging especially in small biopsy samples. HEY1-NCOA2 fusion transcript has been identified in more than 90% of mesenchymal chondrosarcoma, but not in other soft tissue tumors.

**Useful For:** Supporting a diagnosis of mesenchymal chondrosarcoma when pathological examination is insufficient for diagnosis.

**Interpretation:** A HEY1-NCOA2 fusion transcript positive result supports a diagnosis of mesenchymal chondrosarcoma but a negative result does not necessarily rule-out a diagnosis of mesenchymal chondrosarcoma.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**Mesoridazine (Serentil)**

**Reference Values:**
Reference Range: 150 - 1000 ng/mL

**Mesquite, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
**Class IgE kU/L**  
**Interpretation**

0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4 Positive
4  17.5-49.9 Strongly positive
5  50.0-99.9 Strongly positive
6  > or =100 Strongly positive  
Reference values apply to all ages.


**METF 58123**

**MET (7q31), FISH, Tissue**

**Clinical Information:** MET is a proto-oncogene and its overexpression is associated with disease progression. Recent studies have shown MET amplification to be a major mechanism of acquired resistance to epidermal growth factor receptor tyrosine kinase domain inhibitor (EGFR-TKI). MET amplification has been reported in approximately 5% of patients not treated with EGFR-TKI and up to 20% of patients with acquired resistance to gefitinib or erlotinib.

**Useful For:** Providing prognostic information and guiding treatment primarily for patients with lung, gastric, and renal tumors as well as other tumor types

**Interpretation:** A positive result is detected when the MET:D7Z1 ratio is > or =2.0. The MET locus is reported as amplified when the MET:D7Z1 ratio of 2.0 or greater. Patients with 5 or more copies of MET have a poor prognosis. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**  
An interpretive report will be provided.


**MSNP 64363**

**Metabolic/Syndromic Neuropathy Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Additionally, peripheral neuropathy may be part of an inherited systemic syndromic or metabolic disorder caused by genes in metabolic
pathways. Given the considerable phenotypic overlap and the broad genetic heterogeneity of inherited peripheral neuropathies, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this group of inherited diseases. See Targeted Genes Interrogated by Metabolic/Syndromic Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosis of an inherited metabolic or syndromic neuropathy associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited metabolic or syndromic neuropathy genes where negative Identifying mutations within genes known to be associated with inherited metabolic or syndromic neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Metanephrines, Fractionated, 24 Hour, Urine**

**Clinical Information:** Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating (“spells”). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. In patients that are highly suspect for pheochromocytoma it may be best to screen by measuring plasma free fractionated metanephrines (a more sensitive assay). The 24-hour urinary fractionated metanephrines (a more specific assay) may be used as the first test for low suspicion cases and also as a confirmatory study in patients with <2-fold elevation in plasma free fractionated metanephrines. This is highly desirable, as the very low population incidence rate of pheochromocytoma (<1:100,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures. Complete 24-hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."

**Useful For:** A first- and second-order screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas Confirming positive plasma metanephrine results

**Interpretation:** Increased metanephrine/normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Total urine metanephrines < or =1,300 mcg/24 hours can be detected in nonpheochromocytoma hypertensive patients. Further clinical investigation (eg, radiographic studies) are warranted in patients whose total urinary metanephrine levels are >1,300 mcg/24 hours (approximately 2 times the upper limit of normal). For patients with total urinary metanephrine levels of <1,300 mcg/24 hours further investigations may also be indicated if either the normetanephrine or the metanephrine fraction of the total metanephrines exceed their respective upper limit for hypertensive patients. Finally repeat testing or further investigations may occasionally be
indicated in patients with urinary metanephrine levels below the hypertensive cutoff, or even normal levels, if there is a very high clinical index of suspicion.

**Reference Values:**

**METANEPHRINE**

**Males**

Normotensives

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8 years</td>
<td>29-92 mcg/24 hours</td>
</tr>
<tr>
<td>9-12 years</td>
<td>59-188 mcg/24 hours</td>
</tr>
<tr>
<td>13-17 years</td>
<td>69-221 mcg/24 hours</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>44-261 mcg/24 hours</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are <36 months of age.

**Hypertensives:** <400 mcg/24 hours

**Females**

Normotensives

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8 years</td>
<td>18-144 mcg/24 hours</td>
</tr>
<tr>
<td>9-12 years</td>
<td>43-122 mcg/24 hours</td>
</tr>
<tr>
<td>13-17 years</td>
<td>33-185 mcg/24 hours</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>30-180 mcg/24 hours</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are <36 months of age.

**Hypertensives:** <400 mcg/24 hours

**NORMETANEPHRINE**

**Males**

Normotensives

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8 years</td>
<td>34-169 mcg/24 hours</td>
</tr>
<tr>
<td>9-12 years</td>
<td>84-422 mcg/24 hours</td>
</tr>
<tr>
<td>13-17 years</td>
<td>91-456 mcg/24 hours</td>
</tr>
<tr>
<td>18-29 years</td>
<td>103-390 mcg/24 hours</td>
</tr>
<tr>
<td>30-39 years</td>
<td>111-419 mcg/24 hours</td>
</tr>
<tr>
<td>40-49 years</td>
<td>119-451 mcg/24 hours</td>
</tr>
<tr>
<td>50-59 years</td>
<td>128-484 mcg/24 hours</td>
</tr>
<tr>
<td>60-69 years</td>
<td>138-521 mcg/24 hours</td>
</tr>
<tr>
<td>&gt; or =70 years</td>
<td>148-560 mcg/24 hours</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are <36 months of age.

**Hypertensives:** <900 mcg/24 hours

**Females**

Normotensives

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8 years</td>
<td>29-145 mcg/24 hours</td>
</tr>
<tr>
<td>9-12 years</td>
<td>55-277 mcg/24 hours</td>
</tr>
<tr>
<td>13-17 years</td>
<td>57-286 mcg/24 hours</td>
</tr>
<tr>
<td>18-29 years</td>
<td>103-390 mcg/24 hours</td>
</tr>
<tr>
<td>30-39 years</td>
<td>111-419 mcg/24 hours</td>
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</tr>
<tr>
<td>60-69 years</td>
<td>138-521 mcg/24 hours</td>
</tr>
<tr>
<td>&gt; or =70 years</td>
<td>148-560 mcg/24 hours</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are <36 months of age.

**Hypertensives:** <900 mcg/24 hours

**TOTAL METANEPHRINE**

**Males**

Normotensives

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8 years</td>
<td>47-223 mcg/24 hours</td>
</tr>
<tr>
<td>9-12 years</td>
<td>201-528 mcg/24 hours</td>
</tr>
<tr>
<td>13-17 years</td>
<td>120-603 mcg/24 hours</td>
</tr>
<tr>
<td>18-29 years</td>
<td>190-583 mcg/24 hours</td>
</tr>
<tr>
<td>30-39 years</td>
<td>200-614 mcg/24 hours</td>
</tr>
</tbody>
</table>

Reference values have not been established for patients that are <36 months of age.

**Hypertensives:** <900 mcg/24 hours
Metanephrines, Fractionated, Free, Plasma

**Clinical Information:** Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine (collectively referred to as metanephrines) are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. The metanephrines are stable metabolites and are cosecreted directly with catecholamines by pheochromocytomas and other neural crest tumors. This results in sustained elevations in plasma free metanephrine levels, making them more sensitive and specific than plasma catecholamines in the identification of pheochromocytoma patients. Metanephrine and normetanephrine are both further metabolized to conjugated metanephrines and vanillylmandelic acid.

**Useful For:** Screening test for presumptive diagnosis of catecholamine-secreting pheochromocytomas or paragangliomas

**Interpretation:** In the normal population, plasma metanephrine and normetanephrine levels are low, but in patients with pheochromocytoma or paragangliomas, the concentrations may be significantly elevated. This is due to the relatively long half-life of these compounds, ongoing secretion by the tumors and, to a lesser degree, peripheral conversion of tumor-secreted catecholamines into metanephrines. Measurement of plasma free metanephrines appears to be the best test for excluding pheochromocytoma. The test's sensitivity approaches 100%, making it extremely unlikely that individuals with normal plasma metanephrine and normetanephrine levels suffer from pheochromocytoma or paraganglioma. Due to the low prevalence of pheochromocytomas and related tumors (<1:100,000), it is recommended to confirm elevated plasma free metanephrines with a second, different testing strategy in order to avoid large numbers of false-positive test results. The recommended second-line test is measurement of fractionated 24-hour urinary metanephrines (METAF / Metanephrines, Fractionated, 24 Hour, Urine). In most cases this strategy will suffice in confirming or excluding the diagnosis. Occasionally, it will be
necessary to extend this approach if there is a very high clinical index of suspicion or if test results are nonconclusive. In these cases, repeat plasma and urinary metanephrines testing, additional measurement of plasma or urinary catecholamines, or imaging procedures might be indicated. Elevated results are reported with appropriate comments.

**Reference Values:**

**METANEPHRINE, FREE**

<0.50 nmol/L

**NORMETANEPHRINE, FREE**

<0.90 nmol/L

**Clinical References:**


**Clinical Information:**

Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating (“spells”). Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine and norepinephrine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. While screening for pheochromocytoma is best accomplished by measuring plasma free fractionated metanephrines (a more sensitive assay), follow-up testing with urinary fractionated metanephrines (a more specific assay) may identify false-positives. Twenty-four hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."

**Useful For:**

A second-order screening test for the presumptive diagnosis of pheochromocytoma in patients with nonepisodic hypertension Confirming positive plasma metanephrine results in patients with nonepisodic hypertension

**Interpretation:**

Increased metanephrine/normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Increased urine metanephrines can be detected in nonpheochromocytoma hypertensive patients; quantification may help distinguish these patients from those with tumor-induced symptoms.

**Reference Values:**

**METANEPHRINE/CREATININE**

<table>
<thead>
<tr>
<th>Normotensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years: 82-418 mcg/g creatinine</td>
</tr>
<tr>
<td>3-8 years: 65-332 mcg/g creatinine</td>
</tr>
<tr>
<td>9-12 years: 41-209 mcg/g creatinine</td>
</tr>
<tr>
<td>13-17 years: 30-154 mcg/g creatinine</td>
</tr>
<tr>
<td>&gt; or =18 years: 29-158 mcg/g creatinine</td>
</tr>
</tbody>
</table>

**NORMETANEPHRINE/CREATININE**

<table>
<thead>
<tr>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensives</td>
</tr>
<tr>
<td>0-2 years: 82-418 mcg/g creatinine</td>
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<td>13-17 years: 30-154 mcg/g creatinine</td>
</tr>
<tr>
<td>&gt; or =18 years: 29-158 mcg/g creatinine</td>
</tr>
</tbody>
</table>
### TOTAL METANEPHRINE/CREATININE

#### Males

**Normotensives**

- **0-2 years**: 241-1,272 mcg/g creatinine
- **3-8 years**: 186-980 mcg/g creatinine
- **9-12 years**: 110-582 mcg/g creatinine
- **13-17 years**: 78-412 mcg/g creatinine
- **18-29 years**: 96-286 mcg/g creatinine
- **30-39 years**: 106-316 mcg/g creatinine
- **40-49 years**: 117-349 mcg/g creatinine
- **50-59 years**: 130-386 mcg/g creatinine
- **60-69 years**: 143-427 mcg/g creatinine
- **> or =70 years**: 159-472 mcg/g creatinine

#### Females

**Normotensives**

- **0-2 years**: 241-1,272 mcg/g creatinine
- **3-8 years**: 186-980 mcg/g creatinine
- **9-12 years**: 110-582 mcg/g creatinine
- **13-17 years**: 78-412 mcg/g creatinine
- **18-29 years**: 131-467 mcg/g creatinine
- **30-39 years**: 147-523 mcg/g creatinine
- **40-49 years**: 164-585 mcg/g creatinine
- **50-59 years**: 184-655 mcg/g creatinine
- **60-69 years**: 206-733 mcg/g creatinine
- **> or =70 years**: 230-821 mcg/g creatinine

### Clinical References:

**Metformin, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

**Synonym(s):** Glucophage

Therapeutic range: Approximately 1â€“2 mcg/mL. Metformin associated lactic acidosis generally has been associated with Metformin plasma concentrations exceeding 5 mcg/mL.

**Methadone and Metabolites, Serum**

**Clinical Information:** Methadone, a long-acting synthetic opioid analgesic, is an agonist at the mu receptor. It has several actions qualitatively similar to those of morphine, primarily involving the central nervous system and organs composed of smooth muscles. Analgesia, sedation, and detoxification or maintenance in opioid addiction can be achieved with therapeutic use of methadone hydrochloride. Methadone acts by binding to the mu-opioid receptor, but also has some affinity for the N-methyl-D-aspartate receptor (NMDA) ionotropic glutamate receptor. Methadone undergoes extensive biotransformation in the liver. Methadone is metabolized by CYP3A4, CYP2B6, CYP2C19, CYP2D6, and is a substrate for the P-glycoprotein efflux protein. The major inactive metabolite is a result of N-demethylation and cyclization, and forms 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Substantial interindividual and intraindividual variability in metabolism and elimination has been noted. The half-life of methadone is highly variable and typically ranges from 7 to 59 hours, however, longer half-lives have been reported.

**Useful For:** Compliance monitoring of methadone

**Interpretation:** There is a significant overlap between the reported therapeutic and toxic concentrations of methadone in blood specimens.

**Reference Values:** Not established


**Methadone Confirmation, Chain of Custody, Urine**

**Clinical Information:** Methadone (dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin.(1) Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6.(1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved.(1-5)
Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). (1-4) The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys. (1,4) Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH. (5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy. (5) Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine. (7) This is commonly referred to as "spiking." In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP. (7) The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Monitoring of methadone treatment for analgesia or drug rehabilitation Urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is particularly useful for assessing compliance with rehabilitation programs. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of >0.60. (6) An EDDP:methadone ratio <0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen. (7)

**Reference Values:**

**Negative**

Cutoff concentrations:

**IMMUNOASSAY SCREEN**

<300 ng/mL

**METHADONE BY GC-MS**

<100 ng/mL

**2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE BY GC-MS**

<100 ng/mL

Methadone Confirmation, Urine

Clinical Information: Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin. (1) Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6. (1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved. (1-5) Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). (1-4) The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys. (1,4) Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH. (5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy. (5) Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine. (7) This is commonly referred to as “spiking.” In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP. (7) The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen.

Useful For: Monitoring of methadone treatment for analgesia or drug rehabilitation Urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is particularly useful for assessing compliance with rehabilitation programs.

Interpretation: The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of >0.60. (6) An EDDP:methadone ratio <0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen. (7)

Reference Values:
Negative
Cutoff concentrations:

METHADONE BY GC-MS
<100 ng/mL

2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE BY GC-MS
<100 ng/mL


**FMETH**

**Methaqualone Confirmation, urine**

**Interpretation:** Methaqualone, ng/mL Report Limit 50 ng/mL Reference Range 500-80000 ng/mL Critical Value â€” High 160000 ng/mL

**Reference Values:**

ng/mL

Results are reported to the limit of quantitation for the analysis.

**MET**

**Methemoglobin and Sulfhemoglobin, Blood**

**Clinical Information:** Methemoglobin: When iron in hemoglobin is oxidized from the normal divalent state to a trivalent state, the resulting brownish pigment is methemoglobin. Methemoglobin cannot combine reversibly with oxygen and is associated with cyanosis. Methemoglobinemia, with or without sulfhemoglobinemia, is most commonly encountered as a result of administration of medications such as phenacetin, phenazopyridine, sulfonamides, local anesthetics, dapsone, or following ingestion of nitrates or nitrates. Congenital methemoglobinemias are rare. They are either due to: -Deficiency of methemoglobin reductase (also called cytochrome B5 reductase or diaphorase) in erythrocytes, an autosomal recessive disorder. -One of several intrinsic structural disorders of hemoglobin, called methemoglobin-M, all of which are inherited in the autosomal dominant mode. Methemoglobinemia responds to treatment with methylene blue or ascorbic acid. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. Sulfhemoglobinemia is associated with cyanosis and often accompanies drug-induced methemoglobinemia. Sulfhemoglobinemia can be due to exposure to trinitrotoluene or zinc ethylene bisdithiocarbamate (a fungicide), or by ingestion of therapeutic doses of flutamide. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, blood level of sulfhemoglobin declines gradually over a period of weeks. Patients with sulfhemoglobinemia often also have methemoglobinemia. There is no specific treatment for sulfhemoglobinemia. Therapy is directed at reversing the methemoglobinemia, if present.

**Useful For:** Diagnosing methemoglobinemia and sulfhemoglobinemia Identifying cyanosis due to other causes, such as congenital heart disease

**Interpretation:** In congenital methemoglobinemia, the methemoglobinemia concentration in blood is about 15% to 20% of total hemoglobin. Such patients are mildly cyanotic and asymptomatic. In acquired (toxic) methemoglobinemia, the concentration may be much higher. Symptoms may be severe when methemoglobin is >40% of hemoglobin. Very high concentrations (>70%) may be fatal.

**Reference Values:**

**METHEMOGLOBIN**

0-11 months: not established

> or =1 year: 0.0-1.5% of total hemoglobin

**SULFHEMOGLOBIN**

0-11 months: not established

> or =1 year: 0.0-0.4% of total hemoglobin

**Methemoglobin Reductase, Blood**

**Clinical Information:** Methemoglobin reductase, also called "diaphorase," and more properly called cytochrome b5 reductase, is the enzyme within the erythrocyte that maintains hemoglobin in the reduced (non-methemoglobin) state. Persons who are heterozygous for methemoglobin reductase mutations have no clinical or laboratory abnormalities, are not cyanotic, and have normal methemoglobin concentrations in their blood. However, they hold an increased risk for more severely symptomatic acute episodes of methemoglobinemia with exposure to inducing agents. Persons who are homozygous for methemoglobin reductase mutations have normal arterial oxygen saturation but have varying quantities of methemoglobin in their blood, generally 15% to 20%, and are quite cyanotic. Paradoxically, homozygotes typically have normal blood counts; the condition only rarely causes polycythemia. The presence of methemoglobin shifts the hemoglobin-O2 dissociation curve to the right, so that although the transport of oxygen is diminished, the delivery of oxygen to tissues is normal. Because of the chronicity, the homozygous condition is usually compensated and therefore quite benign, but may cause concern to parents of affected children, be a cosmetic embarrassment to the children, and alarm the attending physician. The cyanosis may be treated with methylene blue.

**Useful For:** Confirming cases of suspected methemoglobin reductase (cytochrome b5 reductase) deficiency Functional studies in families with methemoglobin reductase (cytochrome b5 reductase) deficiency

**Interpretation:** Methemoglobin reductase (cytochrome b5 reductase) activity in neonates (0-6 weeks) is normally 60% of the normal adult value. Adult values are attained by 2 to 3 months of age. Heterozygotes have results slightly lower than the reference range. Homozygotes demonstrate little to no methemoglobin reductase activity and increased levels of methemoglobin.

**Reference Values:**
- > or =12 months: 6.6-13.3 U/g Hb
- Reference values have not been established for patients who are <12 months of age.


**Methemoglobinemia Evaluation**

**Clinical Information:** Methemoglobin: Methemoglobinemia, with or without sulfhemoglobinemia, is most commonly encountered as a result of administration of such medications as phenacetin, phenazopyridine, sulfonamides, local anesthetics, dapsone, or following ingestion of nitrates or nitrites. Congenital methemoglobinemias are rare. They are due either to: -A deficiency of methemoglobin reductase (also called cytochrome B5 reductase or diaphorase) in erythrocytes, an autosomal recessive disorder -One of several intrinsic structural disorders of hemoglobin, called methemoglobin-M, all of which are inherited in the autosomal dominant mode Sulfhemoglobin: Sulfhemoglobinemia often accompanies methemoglobinemia. Sulfhemoglobinemia can be due to exposure to trinitrotoluene and/or zinc ethylene bisdithiocarbamate (a fungicide). The formation of sulfhemoglobin cannot be reversed and there is no therapy for sulfhemoglobinemia. Because patients with sulfhemoglobinemia also often have methemoglobinemia, therapy is directed at reversing the methemoglobinemia present. Symptoms of both methemoglobinemia and sulfhemoglobinemia are caused by anoxia and are characterized by cyanosis.

**Useful For:** Diagnosis of methemoglobinemia and sulfhemoglobinemia Differentiation of methemoglobinemia and sulfhemoglobinemia from other causes of cyanosis (eg, congenital heart disease)

**Interpretation:** In congenital methemoglobinemia, the methemoglobin concentration in blood is about 15% to 20% of total hemoglobin. Such patients are mildly cyanotic and asymptomatic. In acquired (toxic) methemoglobinemia, the concentration may be much higher. Symptoms may be severe when methemoglobin is >40% of hemoglobin. Very high concentrations may be fatal. This is a consultative evaluation in which the history and previous laboratory values are reviewed by a hematologist who is an expert on these disorders. Appropriate tests are performed and an interpretive report is issued.
Reference Values:
Definitive results and an interpretive report will be provided.


**MTXSG 62580**

**Methotrexate Post Glucarpidase, Serum**

**Clinical Information:** Methotrexate, an antimetabolite (folate reductase inhibitor), is used at high dose (12 gm/m²) to treat neoplastic diseases, such as lymphocytic leukemia. Therapy is guided by measurement of serum concentration: 24 hours after dosage, the serum concentration should be <10 mcmol/L; 48 hours after therapy, concentration should be <1 mcmol/L; and 72 hours after dosage, the concentration should be <0.1 mcmol/L or <0.05 mcmol/L, depending on clinical protocol. It is also administered at low dose (a single dose of 5-15 mg per week) to treat severe psoriasis and rheumatoid arthritis. Methotrexate is 65% orally bioavailable. Peak serum concentrations are reached 2 to 3 hours after dosing. Protein binding is approximately 45%. Volume of distribution is 0.4 L/kg. Elimination is concentration dependent with an apparent elimination half-life of 1.8 hours when the serum concentration is >1 mcmol/L, 8 hours when between 0.1 and 1 mcmol/L, and approximately 30 hours when <0.1 mcmol/L. Voraxaze (glucarpidase) is a carboxypeptidase enzyme indicated for the treatment of toxic plasma methotrexate (MTX) concentrations (>1 mcmol/L) in patients with delayed methotrexate clearance due to impaired renal function. Measurement of methotrexate using immunoassays is unreliable for specimens collected within 48 hours following Voraxaze administration since it can result in falsely elevated results. As a result, this liquid chromatography-tandem mass spectrometry assay should be used to monitor MTX concentrations postglucarpidase therapy.

**Useful For:** Monitoring methotrexate concentrations postglucarpidase therapy

**Interpretation:** Following a 4 to 6 hour intravenous infusion of methotrexate, postinfusion concentrations greater than the following indicate an increased risk of toxicity if conventional low-dose leucovorin rescue is given: -24-hour postinfusion concentration: 5.0 to 10.0 mcmol/L -48-hour postinfusion concentration: 0.5 to 1.0 mcmol/L -72-hour postinfusion concentration: 0.1 mcmol/L

**Reference Values:**
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L


**MTHX 37047**

**Methotrexate, Serum**

**Clinical Information:** Methotrexate is an antineoplastic agent that inhibits DNA synthesis. The drug exerts its effects through competitive inhibition of the enzyme dihydrofolate reductase thus decreasing the concentrations of tetrahydrofolate essential to the methylation of pyrimidine nucleotides and consequently the rate of pyrimidine nucleotide and ultimately DNA synthesis. Methotrexate is used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Methotrexate is effective against malignancies characterized by rapid cell proliferation. Intermediate to high doses of methotrexate with leucovorin (citrovorum-factor or folinic acid) rescue to salvage nontumor cells have been used with favorable results in the treatment of osteogenic sarcoma, leukemia, non-Hodgkin lymphoma, lung, and breast cancer. Methotrexate has the potential for serious toxicity. Patients undergoing methotrexate therapy are closely monitored so that toxic effects are detected promptly.

**Useful For:** Following therapy, serum concentration is used to judge whether the drug is being cleared appropriately and verify that a nontoxic concentration has been attained

**Interpretation:** Serum concentrations of methotrexate are commonly monitored during high-dose therapy (>50 mg/m²) to identify the time at which active intervention by leucovorin rescue should be
initiated. Criteria for serum concentrations indicative of a potential for toxicity after single-bolus, high-dose therapy are as follows: -Methotrexate >10 mcmol/L 24 hours after dose -Methotrexate >1 mcmol/L 48 hours after dose -Methotrexate >0.1 mcmol/L 72 hours after dose

**Reference Values:**
Non-toxic drug concentration after 72 hours: <0.1 mcmol/L


**FMETX**
Methsuximide (Celontin) as Desmethylmethsuximide

**Reference Values:**
10.0 - 40.0 ug/mL

Methsuximide measured as desmethylmethsuximide.

**METHV**
Methyl Violet, Nrv ST

**Reference Values:**
Report sent under separate cover

**MTHB**
Methylene Blue, Nrv ST

**Reference Values:**
Report sent under separate cover

**MMAAF**
Methylmalonic Acid (MMA), Amniotic Fluid

**Clinical Information:** Methylmalonic acid (MMA) is a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which includes at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities in the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels. Because the morbidity and mortality of methylmalonic acidemia are high, genetic counseling and prenatal diagnosis are frequently sought by families with 1 or more affected children. The prenatal diagnosis is made on a dual, complementary approach: enzymatic assays in cultured amniocytes or molecular analysis for previously identified familial mutations and direct chemical determination of MMA in cell-free supernatant of amniotic fluid from amniocentesis between 16 and 19 weeks of gestational age.

**Useful For:** Specific diagnostic marker for methylmalonic acidemia

**Interpretation:** A significantly increased amniotic fluid methylmalonic acid concentration supports a diagnosis of methylmalonic acidemia.
**Reference Values:**
<1.50 nmol/mL

**Clinical References:**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia. Additional confirmatory testing must be performed. Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency. Several studies have suggested that the determination of plasma or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately time elevated values indicate a likely cobalamin deficiency.

**Reference Values:**
< or =0.40 nmol/mL

**Clinical References:**
Methylmalonic Acid (MMA), Quantitative, Serum

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels.

Useful For: Evaluating children with signs and symptoms of methylmalonic acidemia Additional confirmatory testing must be performed. Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

Interpretation: In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin (vitamin B12) deficiency.

Reference Values:
< or = 0.40 nmol/mL

Clinical References:

Methylmalonic Acid (MMA), Quantitative, Urine

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme
methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, which includes serum and urine MMA levels.

Useful For: Evaluating children with signs and symptoms of methylmalonic acidemia Additional confirmatory testing must be performed Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin deficiency Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

Interpretation: In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin deficiency.

Reference Values:
<3.60 mmol/mol creatinine

Clinical References:

Methylmalonic Aciduria and Homocystinuria, cblC Type, Full Gene Analysis

Clinical Information: Multiple causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 9 distinct complementation classes (cblA-cblH and mut, caused by mutations in the gene encoding methylmalonyl coenzyme A mutase). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both. The most common disorder in this group is methylmalonic aciduria and homocystinuria, cblC (cobalamin C) type, which results in both methylmalonic aciduria and homocystinuria. cblC type is an autosomal recessive disorder with a variable age of onset. In the early onset form, symptoms appear in the first several years of life and include failure to thrive, developmental delay, seizures, metabolic crisis, and hydrocephalus. Patients may also have hemolytic uremic syndrome. Adults can present with confusion or other changes in mental status, cognitive decline, and megaloblastic anemia. Biochemical presentation includes methylmalonic aciduria and homocystinuria in urine organic acid or plasma amino acid analysis. Other complementation class disorders, such as cblD and cblF, can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types. Mutations in the MMACHC gene are responsible for the cblC type disorder. The most common mutation (identified in approximately 40% of mutant alleles) is 271dupA. This multiethnic mutation is most frequently associated with early-onset disease, especially when present in the homozygous state. Another early-onset mutation is R111X, which is common in the Cajun and French Canadian populations. R132X is a late-onset mutation that has been identified in individuals of Indian, Pakistani, and Middle Eastern ethnicity. Although these genotype-phenotype correlations are well-established, there is often considerable variability in age of onset and expression of symptoms, even within families.
Useful For: Confirmation of diagnosis of methylmalonic aciduria and homocystinuria, cblC type
Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified Carrier screening in cases where there is a family history of methylmalonic aciduria and homocystinuria, but disease-causing mutations have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Methylmalonic Aciduria and Homocystinuria, cblD Type, Full Gene Analysis

Clinical Information: Several causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 8 distinct complementation classes (cblA-cblH). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both. cblD type is a rare autosomal recessive disorder with variable clinical presentations. It can present as cblD variant 1, associated with isolated homocystinuria; cblD variant 2, associated with isolated methylmalonic aciduria; or as cblD combined, associated with both methylmalonic aciduria and homocystinuria. cblD variant 1 is associated with clinical features of isolated homocystinuria, including megaloblastic anemia and neurological abnormalities, as well as developmental delays. cblD variant 2 is associated with clinical features of isolated methylmalonic aciduria, including metabolic decomposition, which can result in lethargy, failure to thrive, feeding problems, and hypotonia. cblD combined is associated with clinical features of both methylmalonic aciduria and homocystinuria. Biochemical presentation includes methylmalonic aciduria and/or homocystinuria in urine organic acid or plasma amino acid analysis.(1) Other complementation class disorders can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types. Mutations in the MMADHC gene are responsible for the cblD type disorder. To date, 9 mutations in 7 individuals have been identified.(2) Three missense mutations identified in exons 6 and 8 have been associated with cblD variant 1. One nonsense mutation, 1 in-frame duplication, and 1 frame-shift deletion in exons 3 and 4 have been associated with cblD variant 2. One nonsense mutation, 1 frame-shift duplication, and 1 splice-site deletion in exons 5 and 8 and intron 7 have been associated with cblD combined.

Useful For: Confirmation of diagnosis of disorders belonging to the cblD complementation group Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified Distinguishing between cblA, cblB, and cblD variant 2 when methylmalonic aciduria is identified Carrier screening in cases where there is a family history of methylmalonic aciduria or homocystinuria, but disease-causing mutations have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FMMTU 57796**
Methylphenidate (Ritalin) & MTB, Urine

**Reference Values:**
Reference Range: Not Established
Units: ng/mL

**RIT 80456**
Methylphenidate, Serum

**Reference Values:**
Reference Range: 5.0 - 20.0 ng/mL

**MEX 9245**
Mexiletine, Serum

**Clinical Information:** Mexiletine is a class I B antiarrhythmic with electrophysiologic properties similar to lidocaine and is useful in suppression of ventricular arrhythmias. The drug exhibits a high degree of oral bioavailability, is approximately 60% protein bound, and undergoes renal clearance at a rate of 10.3 mL/min/kg. Mexiletine has a volume of distribution of 9.5 L/kg at a half-life of 11 hours. Myocardial infarction and uremia reduce the rate of clearance and increase the half-life of mexiletine, requiring dosage adjustment guided by drug monitoring. Mexiletine toxicity occurs at concentrations >2.0 mcg/mL (trough value) and is characterized by symptoms of nausea, hypotension, sinus bradycardia, paresthesia, seizures, intermittent left bundle branch block, and temporary asystole.

**Useful For:** Assessing achievement of optimal therapeutic concentrations Assessing potential toxicity

**Interpretation:** Optimal response to mexiletine occurs when the serum concentration is within the range of 0.8 to 2.0 mcg/mL (trough value).

**Reference Values:**
Therapeutic concentration: 0.8-2.0 mcg/mL (trough value)
Toxic concentration: >2.0 mcg/mL (trough value)

**Clinical References:**

**MGMT 36733**
MGMT Promoter Methylation, Tumor

**Clinical Information:** Glioblastoma (WHO Grade IV astrocytoma) is the most frequent malignant primary central nervous system tumor in adults. It has a very poor prognosis, with median survival of less than a year. Current standard of care consists of surgical resection followed by radiotherapy in addition to
alkylating chemotherapy with temozolomide. MGMT (O[6]-methylguanine-DNA methyltransferase) is a DNA repair enzyme. This enzyme rescues tumor cells from alkylating agent-induced damage, and this leads to resistance to chemotherapy with alkylating agents. Epigenetic silencing of the MGMT gene by promoter methylation results in decreased MGMT protein expression, reduced DNA repair activity, and potential increased sensitivity to therapy. MGMT promoter methylation status has been most widely evaluated by methylation-specific PCR method, which is both sensitive and specific. In newly diagnosed glioblastomas, the presence of MGMT promoter methylation has been shown to be an independent favorable prognostic factor and a strong predictor of responsiveness to alkylating chemotherapy (ie, temozolomide). This is particularly relevant for elderly patients (older than 60-65 years), who usually have decreased tolerance for combined aggressive chemoradiation. For this group of patients, recent clinical trials have provided strong evidence supporting an alternative therapeutic strategy consisting of monotherapy with the alkylating agent temozolomide for patients whose tumors show MGMT promoter methylation and radiotherapy alone for patients whose tumors lack MGMT promoter methylation. Thus, in addition to the significant prognostic and predictive value, MGMT methylation status has emerged as a valuable biomarker to guide therapy decision making for newly diagnosed glioblastoma in elderly patients, preventing unnecessary treatment toxicities and costs. MGMT promoter methylation has been reported to high rates in oligodendrogliomas and astrocytomas of lower grade, in which they variably correlate with 1p19q codeletion and IDH mutations. Prognostic and predictive significance of MGMT promoter methylation status in these tumors has been shown in some studies, but not in others.

**Useful For:** Prognostication of newly diagnosed glioblastomas Identifying newly diagnosed glioblastomas that may respond to alkylating chemotherapy (ie, temozolomide) Guidance for therapy decision making for newly diagnosed glioblastomas in elderly patients (older than 60-65 years)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FMI2**

**MI-2**

**Clinical Information:**
MI-2 is a Myositis specific Autoantibody and is seen in 5-10% of adult Dermatomyositis and in 5% of Juvenile Dermatomyositis cases.

**Reference Values:**
Negative

**RMA**

**Microalbumin, Random, Urine**

**Clinical Information:** Diabetic nephropathy is a complication of diabetes and is characterized by proteinuria (normal urinary albumin excretion is <30 mg/day; overt proteinuria is >300 mg/day). Before overt proteinuria develops, albumin excretion increases in those diabetic patients who are destined to develop diabetic nephropathy. Therapeutic maneuvers (eg, aggressive blood pressure maintenance, particularly with angiotensin-converting enzyme inhibitors; aggressive blood sugar control; and possibly
decreased protein intake) can significantly delay, or possibly prevent, development of nephropathy. Thus, there is a need to identify small, but abnormal, increases in the excretion of urinary albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin/creatinine ratio from a random urine specimen is also considered a valid screening tool.(3) Several studies have addressed whether the specimen needs to be a fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

**Useful For:** Assessing the potential for early onset of nephropathy in diabetic patients

**Interpretation:** In random urine specimens, normal urinary albumin excretion is <17 mg/g creatinine for males and <25 mg/g creatinine for females.(2) Microalbuminuria is defined as an albumin/creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin/creatinine of > or =300 is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, first-morning random or 24-hour timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an ACE inhibitor (if the patient can tolerate it).

**Reference Values:**
- Males: <17 mg/g creatinine
- Females: <25 mg/g creatinine

**Clinical References:**

**MA24 9386 Microalbuminuria, 24 Hour, Urine**

**Clinical Information:** Albumin excretion increases in patients who are destined to develop diabetic nephropathy. More importantly, at this phase of increased albumin excretion before overt proteinuria develops, therapeutic maneuvers can be expected to significantly delay, or possibly prevent, development of nephropathy. These maneuvers include aggressive blood pressure maintenance (particularly with angiotensin-converting enzyme inhibitors), aggressive blood sugar control, and possibly decreased protein intake. Thus, there is a need for addressing small amounts of urinary albumin excretion (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation convened an expert panel to recommend guidelines for the management of patients with diabetes and microalbuminuria. These guidelines recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years should have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a 10-hour overnight collection (9 p.m. to 7 a.m.) or a random collection are acceptable. Recent studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement, and it is now suggested that an albumin/creatinine ratio from a random urine specimen is a valid screening tool.(2) Several studies have addressed the question of whether this needs to be a fasting urine, an exercised urine, or an overnight urine specimen. From these studies, it is clear that the first-morning urine specimen is less sensitive, but more specific. A positive result should be confirmed by a first-morning random or 24-hour timed urine specimen. Studies have also
shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

**Useful For:** Evaluating diabetic patients to assess the potential for early onset of nephropathy

**Interpretation:** An albumin excretion rate >30 mg/24 hours is considered to be microalbuminuric. By definition, the upper end of microalbuminuria is thought to be 300 mg/24 hours. Although this level has not been rigorously defined, it is felt that at this level it is more difficult to change the course of diabetic nephropathy. We have established normal values in our laboratory and agree with the 30 mg/24 hour level. A normal excretion rate of 20 mcg/minute has also been established in the literature and is consistent with our data. Thus, microalbuminuria has been defined at 30 to 300 mg/24 hours. The literature has defined the albumin/creatinine ratio (mg/g) <17 as normal for males and <25 for females(2) and is consistent with our normal data. A ratio of albumin to creatinine of > or =300 indicates overt albuminuria. Thus, microalbuminuria has been defined as an albumin/creatinine ratio of 17 to 299 for males and 25 to 299 for females. Due to biologic variability, any patient who has an albumin/creatinine ratio or urinary albumin excretion rate in the positive microalbuminuria range should have this confirmed with a second specimen. If there is discrepancy, a third specimen is recommended. If 2 of 3 results are in the positive microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, aggressive blood pressure control, and institution of therapy with an angiotensin-converting enzyme inhibitor (if the patient can tolerate it).

**Reference Values:**

- 24-Hour excretion: <30 mg/24 hours
- Excretion rate: <20 mcg/min

**Clinical References:**

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**Micropolyspora faeni, IgG Antibodies, Serum**

**Clinical Information:** Micropolyspora faeni is one of the causative agents of hypersensitivity pneumonitis (HP). Other causative microorganisms include Thermoactinomyces vulgaris and Aspergillus fumigatus. The development of HP caused by Micropolyspora faeni is accompanied by an immune response to Micropolyspora faeni antigens with production of IgG antibodies. While the immunopathogenesis of HP is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.(1)

**Useful For:** Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Micropolyspora faeni

**Interpretation:** Elevated concentrations of IgG antibodies to Micropolyspora faeni, Thermoactinomyces vulgaris, or Aspergillus fumigatus in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**

- 0-12 years: < or =4.9 mg/L
- 13-18 years: < or =9.1 mg/L
- >18 years: < or =13.2 mg/L

**Clinical References:**
Microsatellite Instability (MSI), Tumor

**Clinical Information:** Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene has also been associated with HNPCC/Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of bi-allelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal and/or family history of cancer is suggestive of HNPCC/Lynch syndrome. Tumors from individuals with HNPCC/Lynch syndrome demonstrate microsatellite instability (MSI), characterized by numerous alterations in a type of repetitive DNA called microsatellites. Two distinct MSI tumor phenotypes have been described: MSI-H (instability in >30% of microsatellites examined) and MSS/MSI-L (instability in <30% of microsatellites examined). The MSI-H phenotype is associated with germline defects in the MLH1, MSH2, MSH6, or PMS2 genes, and is the primary phenotype observed in tumors from patients with HNPCC/Lynch syndrome.

Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. Most MSI-H tumors show a loss of protein expression for at least 1 of the 4 mismatch repair genes described above. Loss of expression of protein(s) within the tumor is helpful in identifying which corresponding gene(s) to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (eg, financial concerns, specimen requirements). Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of colon cancer or other HNPCC/Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that MSI testing is not a genetic test, but rather helps to stratify the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. Immunohistochemistry is available as an add-on to this test (IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor). If both MSI and IHC are desired, please order the profile test, HNPCC screen (MSIH / IHC Profile â€“Lynch/HNPCC SCreen). See Hereditary
Nonpolyposis Colorectal Cancer Testing Algorithm in Special Instructions for additional information. Evaluation for MSI may also be valuable for clinical decision making. Colon cancers that demonstrate defective DNA mismatch repair (MSI-H) have a significantly better prognosis compared to those with intact mismatch repair (MSS/MSI-L). Additionally, current data indicate that stage II and stage III patients with colon cancers characterized by the presence of defective MMR (MSI-H) may not benefit from treatment with fluorouracil (5-FU) alone or in combination with leucovorin (LV). These findings are most likely to impact the management of patients with stage II disease.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome

Note: Mayo Clinic's preferred screening test (MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPPC) Screen) includes both microsatellite instability (MSI) and Immunohistochemistry (IHC) testing. Evaluation of tumor tissue for clinical decision making purposes given the prognostic implications associated with MSI phenotypes

**Interpretation:** The report will include specimen information, assay information, and interpretation of test results. Microsatellite stable (MSS) is reported as MSS/MSI-L (0 or 1 of 5 markers demonstrating instability) or MSI-H (2 or more of 5 markers demonstrating instability).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal and/or family history of cancer is suggestive of HNPCC/Lynch syndrome. Testing tumors from individuals at risk for HNPCC/Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair within the tumor. Individuals whose tumors demonstrate the presence of defective DNA mismatch repair in the form of microsatellite instability are more likely to have a germline mutation in 1 of the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Tumors from affected individuals usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined), whereas tumors from individuals who do not have HNPCC/Lynch syndrome usually have an MSS/MSI-L phenotype (MSI at <30% of microsatellites examined). Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC/Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these two possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. See Hereditary Nonpolyposis Colorectal Cancer Testing Algorithm in Special Instructions for additional information.

**Useful For:** Identification of individuals at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome

**Interpretation:** The report will include specimen information, assay information, and interpretation of test results. Microsatellite stable (MSS) is reported as MSS/MSI-L (0 or 1 of 5 markers demonstrating instability) or MSI-H (2 or more of 5 markers demonstrating instability).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Clinical Information:** Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and
Encephalitozoon cuniculi and Encephalitozoon hellem that can infect the conjunctiva, respiratory tract, and genitourinary system. Human infections have been reported most frequently in patients with AIDS, but also can occur in other immunocompromised patients, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae and Brachiola species can cause disseminated or organ-specific disease. This assay detects only the most common microsporidia, Enterocytozoon bieneusi and Encephalitozoon species, and not microsporidiosis due to other species. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Detection of Enterocytozoon bieneusi and Encephalitozoon species in stool and urine specimens to support the clinical diagnosis of microsporidiosis

**Interpretation:** A positive result indicates the presence of Enterocytozoon bieneusi and Encephalitozoon species DNA and is consistent with an active or recent infection. Since microsporidia DNA may be present in stool or urine in the absence of clinical symptoms, results should be correlated with clinical presentation. A negative result indicates absence of detectable DNA from Enterocytozoon bieneusi and Encephalitozoon species in the specimen, but does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or may be sporadic. Other tests to consider in the evaluation of a patient presenting with acute or chronic watery diarrhea include cultures or specific assays for bacterial, viral, and parasitic pathogens.

**Reference Values:**

Negative

**Clinical References:**


**Microsporidia Stain**

**Clinical Information:** Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and Encephalitozoon cuniculi and Encephalitozoon hellem, which can infect the conjunctiva, respiratory tract, and genitourinary system. Human infections have been reported most frequently in patients with AIDS, but also can occur in other immunocompromised patients, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae and Brachiola species can cause disseminated or organ-specific disease. Diagnosis of microsporidiosis is traditionally performed by light microscopic examination of stool, urine, and other specimens using a strong trichrome (chromotrope 2R) stain for detection of the characteristic spores. Unfortunately microscopic identification can be challenging due to the small size of the spores (1-4 micrometer) and their resemblance to yeast. Molecular detection using species-specific PCR offers improved sensitivity and specificity and is available for the microsporidia that cause the majority of intestinal and renal infections (ie, Encephalitozoon species and Enterocytozoon bieneusi). The microsporidia stain is reserved for use with other (non-stool and non-urine) specimen sources due to the variety of other species that may be detected outside of the intestinal tract and kidney. The antihelmintic drug, albendazole has been found effective in some infections due to Enterocytozoon bieneusi and Encephalitozoon (Septata) intestinalis.

**Useful For:** Diagnosis of extra-intestinal microsporidiosis involving the lung, skin, and other organs, particularly in immunocompromised hosts Diagnosis of ocular microsporidiosis

**Interpretation:** A positive result suggests an active or recent infection. Results should be correlated with the patient’s clinical presentation and immune status. A negative result indicates absence of
detectable microsporidial spores in the specimen, but does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or shed sporadically.

**Reference Values:**
- **Negative**
- **If positive, reported as Microsporidia detected**

**Clinical References:**

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**FMIDZ 90112 Midazolam (Versed), serum**

**Reference Values:**
- **Reference Range:** 50 - 600 ng/mL

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**FMCG4 57536 Milk Cow IgG4**

**Interpretation:** mcg/mL of IgG4
- **Lower Limit of Quantitation:** 0.15
- **Upper Limit of Quantitation:** 30.0

**Reference Values:**
- **<0.15 mcg/mL**

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

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**MILK 82871 Milk, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the...
concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


**PMLK 82827**

**Milk, Processed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive

**MD17F 35284 Miller-Dieker Syndrome, 17p13.3 Deletion, FISH**

**Clinical Information:** This test is appropriate for individuals with clinical features suggestive of Miller-Dieker syndrome. Miller-Dieker syndrome is associated with a deletion on the short arm of chromosome 17. The syndrome can be suspected in patients with microcephaly and a prominent forehead with vertical skin furrowing and bitemporal narrowing. The phenotype includes type I lissencephaly (cerebral agyria or smooth brain with a 4-layer cortex), profound electroencephalogram (EEG) abnormality, seizures, hypotonia, severe-to-profound mental retardation, and pre- and postnatal growth retardation. Facial features include ptosis (droopy eyelid), upturned nares, long philtrum (vertical groove on the midline of the upper lip) with thin upper lip, mild micrognathia (small jaw), and malformed ears. Heart and kidney defects are common. Most patients die in infancy. High-resolution chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood) are recommended for patients suspected of having Miller-Dieker syndrome to detect the deletion and to rule out other chromosome abnormalities or translocations. FISH studies are also recommended to detect cryptic translocations involving 17p13.3 that are not demonstrated by conventional chromosome studies.

**Useful For:** Establishing a diagnosis of Miller-Dieker syndrome (LIS1-associated lissencephaly) Detecting cryptic rearrangements involving 17p13.3 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern (2 signals) in each metaphase is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe. This is consistent with a diagnosis of 17p13.3 deletion (Miller-Dieker syndrome or type 1 lissencephaly).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FMINT 57885 Mint (Mentha Piperita) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**FMIRT 57749 Mirtazapine (Remeron)**

Current as of July 8, 2016 11:28 am CDT
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1322
Reference Values:
Reference range: 4.0 ¤“ 40.0 ng/mL

Expected steady state trough mirtazapine concentrations in patients receiving recommended daily dosages: 4.0 ¤“ 40.0 ng/mL

Toxic range not established.

ZW199
Misc Alfred I duPont Hospital for Children
Reference Values:
Test Performed By: Alfred I. duPont Hospital for Children
Molecular Diagnostics Laboratory
1600 Rockland Road
Wilmington, DE 19803

ZW200
Misc All Childrens Hospital - Florida
Reference Values:
Test Performed By: All Childrens Hospital - Florida
Dept of Pathology and Laboratory Medicine
801 6th Street South
St. Petersburg, Florida 33701

ZW152
Misc Baylor Cytogenetics Laboratory
Reference Values:
Test performed by: Baylor Cytogenetics Laboratory
2450 Holcombe Blvd
Houston TX 770212024

ZW201
Misc Baylor John Welsh Cardiovascular Diag Lab
Reference Values:
Test Performed By: Baylor College of Medicine John Walsh
Cardiovascular Diagnostics Laboratory
Dept of Pediatric Cardiology
1102 Bates, FC.480.02
Houston, Texas 77030

ZW204
Misc Cincinnati Childrens Hospital Medical Center
Reference Values:
Test Performed By: Cincinnati Childrens Hospital Medical Ctr
Molecular Genetics Lab
3333 Burnet Ave
Cincinnati, OH 45229

ZW179
Misc Medical Neurogenetics, LLC
Reference Values:
Test Performed By: Medical Neurogenetics Lab
Misc Monogram Biosciences, Inc.
Reference Values:
TEST PERFORMED BY: MONOGRAM BIOSCIENCES, INC.
345 OYSTER POINT BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

Misc National Jewish Health Mycobacteriology Test
Reference Values:
Test Performed by: National Jewish Health Mycobacteriology Lab
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

Misc Seattle Children's Hospital Research Foundation
Reference Values:
Test Performed By: Seattle Children's Hospital Research Foundation
Department of Laboratories
4800 Sand Point Way NE
Seattle, WA 98105

Misc Viracor-IBT Laboratories
Reference Values:
Test Performed by: Viracor-IBT Laboratories
1001 NW Technology Dr
Lee's Summit, MO 64086

Miscellaneous Alfred I duPont Gastroenterology
Reference Values:
Test Performed By: Alfred I. duPont Hospital for Children
Nemours Children's Clinic
Division of Gastroenterology/Nutrition
Gastroenterology Laboratory
1600 Rockland Rd.-Research Bldg. Rm 250
Wilmington, DE 19803

Miscellaneous Ambry Genetics
Reference Values:
Test Performed by: Ambry Genetics
100 Columbia No. 200
Aliso Viejo, CA 92656
**Miscellaneous ARUP Testing**

**Reference Values:**
Test Performed by: ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108

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**Miscellaneous Athena Testing**

**Reference Values:**
Test Performed by: Athena Diagnostics
200 Forest Street, 2nd floor
Marlborough, MA 01752

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**Miscellaneous Baylor Institute of Metabolic Disease**

**Reference Values:**
Test Performed by: Baylor Institute of Metabolic Disease
Baylor Research Institute
3812 Elm Street
Dallas, TX 75226

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**Miscellaneous Baylor Medical Genetics Laboratories**

**Reference Values:**
Test Performed by: Baylor Medical Genetics Laboratories
2450 Holcombe Blvd.
Houston, TX 77021

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**Miscellaneous BloodCenter of WI Testing**

**Reference Values:**
Test Performed by: BloodCenter of Wisconsin
638 N. 18th Street
Milwaukee, WI 53233

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**Miscellaneous Cambridge Biomedical**

**Reference Values:**
Test Performed by: Cambridge Biomedical Inc.
1320 Soldiers Field Road
Boston, MA 02135

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**Miscellaneous Center for Genetic Testing at St. Francis**

**Reference Values:**
Test Performed by: Center for Genetic Testing
St. Francis Hosp-Genetics Lab
6161 S. Yale Ave.
Tulsa, OK 74136
Miscellaneous Chemistry Testing
Reference Values:
Varies

Miscellaneous Child Hosp-Philadelphia
Reference Values:
Test Performed by: The Children’s Hospital of Philadelphia
Main Bldg 5th Floor Rm 5NWS55
34th Street and Civic Center Blvd
Philadelphia, PA 19104

Miscellaneous Childrens Hospital of Colorado Testing
Reference Values:
Test Performed by: Childrens Hospital of Colorado
13123 E 16th Ave
Aurora, CO 80045

Miscellaneous Connective Tissue Gene Tests Lab (CTGT)
Reference Values:
Test Performed By: Connective Tissue Gene Tests, LLC
6575 Snowdrift Road, Suite 106
Allentown, PA 18106

Miscellaneous Correlagen Diagnostics
Reference Values:
Test Performed By: Correlagen Diagnostics
3400 Computer Drive, Suite 100
Westborough, MA 01581

Miscellaneous DIANON Systems
Reference Values:
Varies
Test Performed by: DIANON Systems, Inc.
1 Forest Parkway
Shelton, CT 06484

Miscellaneous Esoterix Coagulation
Reference Values:
Varies
Test Performed by: Esoterix Coagulation
8490 Upland Dr
**Miscellaneous Esoterix Genetic Laboratories, LLC - NY Testing**

**Reference Values:**
Test Performed by: Esoterix Genetic NY  
521 West 57th Street  
6th Floor  
New York, NY 10019

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**Miscellaneous Genetic Assays Inc.**

**Reference Values:**
Test Performed By: Genetic Assays, Inc.  
4711 Trousdale Drive  
Suite 209  
Nashville, TN 37220

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**Miscellaneous Genova Diagnostics**

**Reference Values:**
Test Performed by: Genova Diagnostics  
63 Zillicoa Street  
Asheville, NC 28801-1074

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**Miscellaneous Harvard Medical School**

**Reference Values:**
Test Performed by: Harvard Medical School and Partners Healthcare Laboratory for Molecular Medicine, Center for Genetics and Genomics  
65 Landsdowne Street  
Cambridge, MA 02139

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**Miscellaneous Joli Diagnsotics, Inc.**

**Reference Values:**
Test Performed by: Joli Diagnostic  
2451 Wehrle Drive  
Williamsville, NY 14221

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**Miscellaneous Knight Diagnostic Laboratories**

**Reference Values:**
Test Performed by: Knight Diagnostic Laboratories  
2525 S.W. 3rd Ave.  
Portland, OR 97201-3098
ZW207  Miscellaneous MD Anderson Cancer Center
Reference Values:
Test Performed By: MD Anderson Cancer Center
    Division of Laboratory Medicine
    1515 Holcombe Boulevard
    Houston, TX  77030

ZW79  Miscellaneous Med Coll of WI
Reference Values:
Test Performed by: Medical College of WI
    MACC Fund Research Center, Room 5035
    Dr. Nita Salzman, M.D., Ph.D.
    8701 Watertown Plank Road
    Milwaukee, WI 53226

ZW78  Miscellaneous Medical Coll of WI
Reference Values:
Test Performed by: Medical College of WI
    MACC Fund Research Center, Room 5068
    Jordan N. Fink, M.D.
    Allergy-Immunology Diagnostic Lab
    8701 Watertown Plank Road
    Milwaukee, WI 53226

ZW223  Miscellaneous Metabolite Laboratories, Inc.
Reference Values:
Test Performed by: Metabolite Laboratories, Inc.
    Department of Hematology
    Univ of CO Denver
    12700 E. 19th Ave., Room 9122/9125
    Building P-15, Research Complex 2
    Aurora, CO 80045

ZW2  Miscellaneous MML Referral Test 2
Clinical Information: NA
Reference Values:
Varies with test

ZW3  Miscellaneous MML Referral Test 3
Reference Values:
Vary with test requested.

ZW209  Miscellaneous MRT Laboratories
Reference Values:
Test Performed By: MRT Laboratories
50 Johnson Ave.
Hackensack, NJ 07601

ZW85
90524
Miscellaneous National Jewish Health
Reference Values:
Test Performed by: National Jewish Health
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

ZW211
91858
Miscellaneous Ohio State Univ Molecular Pathology
Reference Values:
Test Performed By: Ohio State University Molecular Pathology Laboratory
173 Hamilton Hall
1645 Neil Avenue
Columbus, OH 43210

ZW214
91861
Miscellaneous Oregon Health and Science University Ocular Immunology Laboratory
Reference Values:
Test Performed By: Oregon Health and Science University Ocular Immunology Laboratory
Casey Eye Institute, BRB Room 253
3181 SW Sam Jackson Road
Portland, OR 97239

ZW129
75137
Miscellaneous Pacific Rim Pathology Medical Corp
Reference Values:
Test Performed by: Pacific Rim Pathology Medical Corp.
5325 Metro St. STE A
San Diego, CA 92110-2608

ZW194
91602
Miscellaneous Prevention Genetics Lab
Reference Values:
Test Performed By: Prevention Genetics Lab
Diagnostics Lab
3700 Downwind Drive
Marshfield, WI 54449

ZW96
90535
Miscellaneous Quest Diagnostics Valencia
Reference Values:
Test Performed by: Quest Diagnostics Nichols Institute
27027 Tourney Rd.
**Miscellaneous RFFIT Testing**

Reference Values:
Test Performed by: RFFIT/K-State Rabies Laboratory
Manhattan/K-State Innovation Center
2005 Research Park Circle
Manhattan, KS 66502

**Miscellaneous Studies Using Chromosome-Specific Probes, FISH**

Clinical Information: Conventional cytogenetic studies can identify the presence of chromosome abnormalities and most mosaic conditions. In approximately 2% of these chromosomally abnormal cases, the genetic makeup of the chromosome abnormality can be identified, but not completely characterized, by conventional techniques alone. For malignant disorders, the proportion of specimens with unresolved chromosome abnormalities is much higher. Chromosomal microarray analysis (CMA) can detect copy number gain or loss of a chromosomal region but cannot identify the mechanism. FISH using gene-specific probes and various probe strategies can help characterize chromosome abnormalities. This includes abnormalities that cannot be accurately characterized by chromosome analysis or CMA such as unusual structural alterations, and unbalanced chromosome abnormalities such as deletions, duplications, and translocations. Scoring large numbers of interphase nuclei can more accurately establish the frequency of chromosome abnormalities and assess level of mosaicism.

Useful For: Resolution of unusual or complex structural alterations, questionable mosaicism, and unbalanced chromosome abnormalities that cannot be resolved by chromosome or chromosomal microarray analysis Identifying gain, loss, or rearrangement of chromosome regions using gene or locus-specific probes

Interpretation: An interpretive report is provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

**Miscellaneous Transgenomic**

Reference Values:
Test Performed by: Transgenomic
5 Science Park
New Haven, CT 06511

**Miscellaneous Tulane University - Matrix DNA Diagnostics**
Reference Values:
Test Performed By: Center for Gene Therapy
Matrix DNA Diagnostics
Tulane University Health Science Center
1430 Tulane Ave, TB28, Tidewater 2140
New Orleans, LA 70112

ZW99
90538
Miscellaneous Univ of AL Testing
Reference Values:
Test Performed by: University of Alabama-Birmingham
648 Kaul Building
720 20th Street South
Birmingham, AL 35233

ZW210
91857
Miscellaneous Univ of IA Molecular Otolaryngology
Reference Values:
Test Performed By: Univ of IA Molecular Otolaryngology
Research Laboratory
5270 Carver Biomedical Research Building
Iowa City, IA 52242

ZW186
91515
Miscellaneous University of Chicago Genetics Services
Reference Values:
Test Performed by: University of Chicago Genetics Services
5841 S. Maryland Ave.
Room 035, M/C 0077
Chicago, IL 60637

ZW187
91514
Miscellaneous University of Iowa Diagnostic Labs
Reference Values:
Test Performed by: UI Diagnostic Laboratories
Department of Pathology
200 Hawkins Drive, Rm 5231 RCP
Iowa City, IA 52242

ZW61
90500
Miscellaneous University of Minnesota Outreach Laboratory
Reference Values:
Test Performed by: Univ of MN Outreach Laboratories
420 Delaware St. S.E.
Minneapolis, MN 55455

ZW191
91599
Miscellaneous University of Texas Health Center at Tyler Microbiology
Reference Values:
Test Performed By: University of Texas Health Center
Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant inherited cancer syndrome that predisposes individuals to the development of colorectal, endometrial, gastric, upper urinary tract, and other cancers. Individuals with HNPCC/Lynch syndrome have a germline mutation in 1 of several genes involved in DNA mismatch repair. The majority of mutations associated with HNPCC/Lynch syndrome occur in MSH2 and MLH1; however mutations in MSH6 and PMS2 have also been identified. There are several strategies for evaluating individuals whose personal and/or family history of cancer is suggestive of HNPCC/Lynch syndrome. Typically, the first step is to evaluate tumors for the characteristics common to individuals with HNPCC/Lynch syndrome which include microsatellite instability (presence of numerous alterations in a type of repetitive DNA called microsatellites) and loss of protein expression of 1 or more of the genes associated with HNPCC/Lynch syndrome. Microsatellite instability (MSI) and immunohistochemistry (IHC) are commonly interpreted together to evaluate risk for HNPCC/Lynch syndrome. High levels of MSI within a tumor are suggestive of defective DNA mismatch repair, however this finding does not provide information about which gene is involved. IHC is a complementary testing strategy used to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in HNPCC/Lynch syndrome related cancers. Loss of expression of 1 or more of these proteins within the tumor is helpful in identifying which corresponding gene(s) to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (eg, financial concerns, specimen requirements). IHC alone can determine retention or loss of MLH1, MSH2, MSH6, and PMS2 protein expression. If all 4 proteins are present, the likelihood of HNPCC/Lynch syndrome is reduced but not eliminated because approximately 5% of tumors that display MSI also have normal protein expression for these 4 genes. Loss of 1 or more proteins by IHC is suggestive of defective DNA mismatch repair within the tumor and the likelihood of HNPCC/Lynch syndrome is increased. Germline testing (ie, mutation analysis) for the corresponding gene(s) can then be performed to identify the causative germline mutation and allow for predictive testing of at risk individuals. Of note, loss of protein expression by IHC has also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and
germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 are observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. See Hereditary Nonpolyposis Colorectal Cancer Testing Algorithm in Special Instructions for additional information.

**Useful For:** Evaluation of tumor tissue to identify patients at risk for having hereditary nonpolyposis colon cancer/Lynch syndrome

**Note:** Mayo's preferred screening test, MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, includes both microsatellite instability and immunohistochemistry testing.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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### Mitochondrial Antibodies (M2), Serum

**Clinical Information:** Antimitochondrial antibodies (AMAs) are detectable by indirect immunofluorescence in >90% of patients with primary biliary cirrhosis (PBC), but this method also detects AMAs of differing specificities in other diseases. The mitochondrial antigens recognized by AMAs in patients' sera have been classified numerically as M1 through M9, with the M2 antigen complex recognized by AMAs in sera from patients with PBC. M2 antigen is comprised of enzyme proteins of the 2-oxoacid dehydrogenase complex that are located on inner mitochondrial membranes. Included in this group of autoantigens are the pyruvate dehydrogenase complex, and 2-oxoglutarate dehydrogenase complex.

**Useful For:** Establishing the diagnosis of primary biliary cirrhosis

**Interpretation:** Positive results for antimitochondrial antibody (AMA) of M2 specificity are highly specific for primary biliary cirrhosis (PBC), and false-negative results are rare. A positive result for AMA of M2 specificity in a patient with clinical features of PBC is virtually diagnostic for this disease.

**Reference Values:**
Negative: <0.1 Units
Borderline: 0.1-0.3 Units
Weakly positive: 0.4-0.9 Units
Positive: > or =1.0 Units
Reference values apply to all ages.

**Clinical References:**
**Clinical Information:** The mitochondrion occupies a unique position in eukaryotic biology. First, it is the site of energy metabolism, without which aerobic metabolism and life as we know it would not be possible. Second, it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to mutations in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involving virtually any organ system, and with widely varying severities. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS) to determine the exact sequence of the entire 16,568 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from mutations in the mitochondrial genome (mtDNA). This includes certain types of myopathies and neuro-opthalomologic diseases, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial myopathy (MM), neurogenic muscle weakness, ataxia, retinitis pigmentosa (NARP), Leigh syndrome, Leber hereditary optic neuropathy (LHON), and chronic progressive external ophthalmoplegia (CPEO). In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayer or Pearson syndromes, are also detected. Mutations in mitochondrial proteins that are encoded by genes in the nucleus, such as the enzymes of fatty acid oxidation, are not detected using this test. In contrast to mutations in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial mutations can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of mutant mitochondria present with more severe disease than those with lower percentages of mutant alleles. The sensitivity for the detection of mutant alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%.

**Useful For:** Diagnosis of the subset of mitochondrial diseases that results from mutations in the mitochondrial genome A second-tier test for patients in whom previous targeted gene mutation analyses for specific mitochondrial disease-related genes was negative Identifying mutations within genes of the mitochondrial genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. The degree of heteroplasmy of each single nucleotide or INDEL variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Large deletions will be reported as either homoplasmic or heteroplasmic, but the degree of heteroplasmy will not be estimated, due to possible preferential amplification of the smaller deletion product by long-range PCR.

**Reference Values:** An interpretive report will be provided.

A final report will be attached in Mayo Access.

**Mitotane (Lysodren)**

**Reference Values:**

Units: ug/mL

Therapeutic and toxic ranges have not been established.

Usual therapeutic doses produce Mitotane serum concentrations of less than 100 ug/mL.

**MLH-1, Immunostain (Bill Only)**

**Reference Values:**

This test is for billing purposes only.
This is not an orderable test.

**MLH1 Gene, Full Gene Analysis**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MLH1 and PMS2 are more likely to have a germline mutation in the MLH1 gene.

**Useful For:** Determining whether absence of MLH1 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer Identification of familial MLH1 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.

Clinical References:

BMLHH 35894
MLH1 Hypermethylation Analysis (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MLHPB 35500
MLH1 Hypermethylation Analysis, Blood

Clinical Information:
Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome/HNPCC, as this leads to inactivation of the MSH2 promoter. Lynch syndrome/HNPCC is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome/HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome/HNPCC spectrum. Several clinical variants of Lynch syndrome/HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome/HNPCC. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and/or immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective mismatch repair in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate...
MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. However, individuals with tumor hypermethylation may additionally have MLH1 promoter hypermethylation consistent with germline inactivation. Individuals with germline inactivation of MLH1 by promoter hypermethylation are at an increased risk for Lynch syndrome/HNPCC-related tumors. In contrast to sequence mutations in MLH1, current evidence suggests that the risk of transmitting germline MLH1 promoter hypermethylation is <50%.

**Useful For:**
As an adjunct to positive hypermethylation in tumor to distinguish between somatic and germline hypermethylation
As an adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates microsatellite instability-H (MSI-H) and loss of MLH1 protein expression

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Interpretive report will be provided.

**Clinical References:**
**Useful For:** An adjunct to MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPPC) Screen, when colon or endometrial tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates MSI-H and loss of MLH1 protein expression. Note: Mayo's preferred screening test (BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor) includes both MLH1 promoter hypermethylation and BRAF V600E testing. Please note that test can only be performed on colon tumors.

**Interpretation:** An interpretive report will be provided. The likelihood of a germline (inherited) mutation is very low in those cases where the tumor demonstrates MLH1 promoter hypermethylation and the normal tissue is unmethylated. The likelihood of a germline mutation is high in those cases where the tumor and normal tissue lack MLH1 promoter hypermethylation. In cases where the tumor and normal tissue demonstrate MLH1 promoter hypermethylation, this result will be interpreted as equivocal and a blood sample will be requested to confirm potential germline hypermethylation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**BRMLH**

**MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor**

**Clinical Information:** Hereditary nonpolyposis colon cancer (HNPPC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in 1 of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6, and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPPC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any 1 of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having HNPPC/Lynch syndrome, especially when testing is performed in conjunction with MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPPC) Screen, which includes MSI1 and IHC studies. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing.
See Hereditary Nonpolyposis Colon Cancer Diagnostic Testing Algorithm in Special Instructions. Also, see Hereditary Colorectal Cancer: Hereditary Nonpolyposis Colon Cancer (November 2005, Communique) in Publications.

Useful For: An adjunct to MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPC) Screen, when colon tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing in cases where colon tumor from the same patient demonstrates MSI-H and loss of MLH1 protein expression.

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


M1M2Z 35492

MLH1/MSH2 Genes, Full Gene Analysis

Clinical Information: Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPPC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. Four genes account for the majority of inherited (germline) mutations: approximately 40% will be associated with a mutation in hMSH2, 40% with a mutation in hMLH1, 10% with a mutation in hMSH6, 5% with a mutation in PMS2, and 5% other (unknown). Data from our laboratory suggests that large deletions, duplications, and other genomic rearrangements may account for approximately 10% and 30% of mutations in hMLH1 and hMSH2, respectively. While the preferred method of testing for Lynch syndrome is to test a tumor from an affected individual for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair, this is not always possible or desired. The MLH1/MSH2 Mutation Screen offers an alternative approach that consists of gene sequencing and array comparative genomic hybridization (aCGH) for the 2 genes most commonly associated with Lynch syndrome. See Hereditary Nonpolyposis Colorectal Cancer Testing Algorithm in Special Instructions for
additional information.

**Useful For:** Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) Detection of mutations in MLH1 and MSH2, the 2 most common genes associated with Lynch syndrome, when microsatellite instability and immunohistochemistry tumor testing is not possible Identification of a familial MLH1 or MSH2 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MLH3 Gene, Full Gene Analysis**

**Clinical Information:** MLH3 is a gene that has been investigated in regards to its role in hereditary colorectal cancer. Current literature suggests that alterations in the MLH3 gene are found more often in the disease population than in healthy controls. Therefore, individuals with a mutation in MLH3 may be at an increased risk for colorectal cancer. However, mutations in MLH3 have been seen in both family members with disease and healthy relatives, indicating reduced penetrance. Also, it has been suggested that MLH3 is a low-risk gene for colorectal cancer. When mutations in MLH3 are seen with mutations in other genes associated with colorectal cancer, the genes may work in an additive manner, further elevating risk. In addition to patients with colorectal cancer, MLH3 alterations have been reported in individuals with endometrial and esophageal cancers. Current literature suggests that in some families MLH3 may act as a low-risk gene for esophageal cancer. Additionally, MLH3 may play a role in endometrial tumorigenesis, with involvement in initiation and/or progression of endometrial cancers. There is conflicting evidence in the literature regarding the ability of mutations in MLH3 to alter mismatch repair (MMR). Some studies suggest that MLH3 mutations can affect DNA mismatch repair, resulting in microsatellite instability (MSI), while others say mutations in MLH3 alone do not interfere with MMR. Alterations have been reported in both microsatellite stable (MSS)/MSI-low tumors and MSI-high tumors. However, some of these MSI-H tumors also had loss reported with immunohistochemistry. Additional research is needed to fully understand the relationship between MLH3 mutations and MSI status.

**Useful For:** Testing for mutations in all 12 exons of the MLH3 gene

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**MLYCD Gene, Full Gene Analysis**

**Clinical Information:** Malonyl-coenzyme A decarboxylase (MCD) deficiency is a rare autosomal recessive inborn error of fatty acid metabolism characterized by reduced activity of mitochondrial malonyl-CoA decarboxylase. This enzyme is responsible for conversion of intramitochondrial malonyl-CoA to acetyl-CoA and carbon dioxide. This leads to an accumulation of malonyl-CoA, which is a strong inhibitor of carnitine palmitoyltransferase-I (CPT-I), an enzyme active in beta-oxidation of fatty acids. The resulting effect is impairment of the breakdown of fatty acids. Isoforms of CPT-I have been found in skeletal and heart muscle, liver, and brain, and symptoms seem to correlate with the localization of these isoforms. The phenotype associated with MCD deficiency is variable, but may include developmental delay, seizures, hypotonia, metabolic acidosis, hypoglycemia, ketosis, and cardiomyopathy. The diagnosis of MCD deficiency is based on the findings of high urinary excretion of malonic acid and a mild increase in dicarboxylic acid. Acylcarnitine analysis by tandem mass spectrometry shows high blood levels of malonylcarnitine (C3DC), which can be detected by neonatal screening before the appearance of symptoms. Determination of MCD activity in cultured fibroblasts can confirm the diagnosis, although this testing is not currently clinically available in the United States. Mutations in the MLYCD gene are responsible for MCD deficiency. The MLYCD gene is located on chromosome 16 and has 5 coding exons. Several different mutations have been described including missense, nonsense, small insertions and deletions, as well as large genomic deletions.

**Useful For:** Confirmation of diagnosis of malonyl-CoA decarboxylase deficiency Carrier screening in cases where there is a family history of malonyl-CoA decarboxylase deficiency, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MMRV Immune Status Profile, Serum**

**Clinical Information:** Measles: The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to <0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011
Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs. The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals. Mumps: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, RSV, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise. Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women. Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens. Rubella: Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, and cardiovascular and ocular defects. The United States 2-dose measles, mumps, and rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. A total of 4 cases of rubella were reported to the CDC in 2011 without any cases of congenital rubella syndrome. Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States. Immunity may however wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella. Varicella-Zoster Virus (VZV): VZV, a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious though typically benign disease usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older, nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV will aid in identifying nonimmune individuals.

**Useful For:** Determination of immune status of individuals to measles, mumps, rubella, and varicella-zoster viruses (VZV)

**Documentation of previous infection with measles, mumps, rubella, or VZV in an individual without a previous record of immunization to these viruses**

**Interpretation:** Positive Measles, Mumps, Varicella-Zoster Viruses (VZV): Antibody Index (AI) Value > or = 1.1 Positive Rubella: AI Value > or = 1.0 The reported Antibody Index (AI) value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cut-off for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies to these viruses indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to measles, mumps, rubella, or VZV are considered...
immune. Equivocal Measles, Mumps, VZV: AI Value 0.9-1.0 Equivocal Rubella: AI Value 0.8-0.9
Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently
vaccinated or if otherwise clinically indicated. Negative Measles, Mumps, VZV: AI Value < or =0.8
Negative Rubella: AI Value < or =0.7 The absence of detectable IgG-class antibodies to measles, mumps,
rubella, or VZV suggests no prior exposure to these viruses or the lack of a specific immune response to
immunization.

Reference Values:
Measles, Mumps and Varicella
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)

Rubella
Vaccinated: Positive (> or =1.0 AI)
Unvaccinated: Negative (< or =0.7 AI)


MOLD1
81878

Mold Panel
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
Reference values apply to all ages.


**MINT** 61696

**Molecular Interpretation**

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**MOLPS** 89270

**Molybdenum, Serum**

**Clinical Information:** Molybdenum is an essential trace element found in the daily diet. It is a cofactor for some enzymes important in nitrogen metabolism (aldehyde dehydrogenase, xanthine oxidase, NADH dehydrogenase). Due to the wide distribution of molybdenum in the environment and particularly in plant materials, molybdenum deficiency is rare in adults with normal, diverse diets. Typical molybdenum intake in most geographic locations is between 45 and 90 mcg/day. Urine is the primary source of excretion, though excesses are sometimes excreted by the biliary route. Molybdenum deficiency associated with parenteral nutrition is indicated by symptoms such as stunted growth, reduced appetite, tachycardia, tachypnea, blindness and coma. These symptoms can be corrected by introducing molybdenum supplementation. Molybdenum cofactor disease is a severe genetic disorder which is due to defective mutations in the MOCS1, MOCS2, and GEPH genes. Molybdenum toxicity is rare and usually related to molybdenum mining exposure; however, it has been observed in cases of intake >400 mcg/day. Molybdenum interferes with copper uptake; molybdenum toxicity is predominantly due to copper deficiency (hypochromic anemia and neutropenia) and inhibition of xanthine oxidase (uric acid accumulation). Serum molybdenum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring of parenteral nutrition Monitoring metallic prosthetic implant wear As an indicator of molybdenum cofactor disease

**Interpretation:** Prosthesis wear is known to result in increased circulating concentrations of metal ions. (5-7) Serum concentrations >10 ng/mL in a patient with molybdenum-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. Serum molybdenum <0.3 ng/mL indicates potential deficiency. Increased serum molybdenum may be seen in acute viral hepatitis, chronic active hepatitis, alcoholic liver disease, and other forms of liver inflammation.

**Reference Values:**
0.3-2.0 ng/mL


FMNM 91829

Monoamine Neurotransmitter Metabolites/Amines

Reference Values:
CSF Metabolite Age related reference ranges (values expressed in nmol/L)

5-Hydroxyindoleacetic acid (5HIAA)
Newborn 0-73 days          208-1159  
Infant 73 days-6 months    179-711
Toddler 6 months-2 years  129-520  
Child 2-5 years            74-345
Older Child 5-10 years    66-338
Adolescent 10-15 years    67-189
Adult > 15 years           67-140

Homovanillic acid (HVA)
Newborn 0-73 days          337-1299  
Infant 73 days-6 months    450-1132
Toddler 6 months-2 years  294-1115  
Child 2-5 years            233-918
Older Child 5-10 years    218-852
Adolescent 10-15 years    167-852
Adult > 15 years           145-852

3-O-methyldopa (3-OMD)
Newborn 0-73 days          0-300  
Infant 73 days-6 months    0-300
Toddler 6 months-2 years  0-300  
Child 2-5 years            0-150
Older Child 5-10 years    0-100
Adolescent 10-15 years    0-100
Adult > 15 years           0-100

MPSU 8823

Monoclonal Protein Study, 24 Hour, Urine

Clinical Information:  Urine proteins can be grouped into 5 fractions by protein electrophoresis:
-Albunin  -Alpha-1  -Alpha-2  -Beta-globulin  -Gamma-globulin The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available in Special Instructions:  
-Laboratory Approach to the Diagnosis of Amyloidosis  -Laboratory Screening Tests for Suspected Multiple Myeloma Also see Diagnosis and Monitoring of Multiple Myeloma in Publications.

Useful For:  Monitoring patients with monoclonal gammopathies

Interpretation:  A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration is followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain.
Immunoglobulin free light chains as well as heavy chain fragments may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of >1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hrs) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) or light chain deposition disease (LCDD). Because patients with AL or LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also performed.

Reference Values:
PROTEIN, TOTAL
<167 mg/24 hours
Reference values have not been established for patients <18 years of age.
Reference values have not been established for patients >83 years of age.
Reference value applies to 24-hour collection.

ELECTROPHORESIS, PROTEIN
If protein concentration is abnormal, the following fractions, if present, will be reported as a percent of the protein, total.
Albumin
Alpha-1-globulin
Alpha-2-globulin
Beta-globulin
Gamma globulin


MPSEX 87997
Monoclonal Protein Study, Expanded Panel, Serum
Clinical Information: Monoclonal proteins are markers of plasma cell proliferative disorders. It has been recommended that serum and urine protein electrophoresis (PEL) and immunofixation electrophoresis (IFE) be performed as the diagnostic algorithm (eg, MPSS / Monoclonal Protein Study, Serum and MPSU / Monoclonal Protein Study, 24 Hour, Urine): A monoclonal band (M-spike) on serum and/or urine PEL identifies a monoclonal process and quantitates the abnormality. IFE characterizes the type of monoclonal protein (gamma, alpha, mu, delta, or epsilon heavy chain; kappa [K] or lambda [L] light chain). IFE is also more sensitive than PEL for detecting small abnormalities that may be present in diseases such as light chain multiple myeloma, oligosecretory myeloma, and plasmacytomas. With the addition of the serum free light chain (FLC) assay, the expanded monoclonal protein study provides even more diagnostic sensitivity for the monoclonal light chain diseases such as primary amyloid and light chain deposition disease—disorders that often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by PEL. The FLC assay is specific for free kappa and lambda light chains and does not recognize light chains bound to intact immunoglobulin. Importantly, the addition of the serum FLC assay to serum PEL and IFE makes the serum diagnostic studies sufficiently sensitive so that urine specimens are no longer required as part of initial diagnostic studies. Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or B lymphocytes (multiple myeloma: MM, macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance: MGUS, smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other laboratory and clinical assessments. If a monoclonal protein pattern is detected by IFE or FLC, a diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been diagnosed, the size of the clonal abnormality can be monitored by PEL and/or FLC and in some instances by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of MGUS, the expanded monoclonal protein study panel provides the information (size of M-spike,
monoclonal protein isotype, FLC K/L ratio) needed for a MGUS progression risk assessment (see Interpretation).

**Useful For:** Diagnosis of monoclonal gammopathies Eliminating the need for urine monoclonal studies as a part of initial diagnostic studies (ie, rule-out monoclonal gammopathy) Assessing risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma

**Interpretation:** Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein. Immunofixation electrophoresis (IFE) is performed to identify the immunoglobulin heavy chain and/or light chain. -A monoclonal IgG or IgA >3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA <3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM >3 g/dL is consistent with macroglobulinemia. -An abnormal serum free light chain (FLC) K/L ratio in the presence of a normal IFE suggests a monoclonal light chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of a serum M-spike >1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike >4 g/dL, >5 g/dL, and >6 g/dL respectively, should be followed by VISCS / Viscosity, Serum. - After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is >0.5 g/dL is considered a significant change. -Patients with monoclonal heavy chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value. -Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IFE. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IFE and/or FLC. Accordingly, a normal serum PEL does not rule out the disease and PEL alone should not be used to screen for the disorder if the clinical suspicion is high. MGUS Prognosis: -Low-risk MGUS patients are defined as having an M-spike <1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of <5%. -High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal PEL Findings: - A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. - A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. - A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. - An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

**Reference Values:**

**PROTEIN, TOTAL**

> or =1 year: 6.3-7.9 g/dL

Reference values have not been established for patients that are <12 months of age.

**PROTEIN ELECTROPHORESIS**

- Albumin: 3.4-4.7 g/dL
- Alpha-1-globulin: 0.1-0.3 g/dL
- Alpha-2-globulin: 0.6-1.0 g/dL
- Beta-globulin: 0.7-1.2 g/dL
- Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report.
IMMUNOFIXATION
No monoclonal protein detected

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO
0.26-1.65

Clinical References:

Monoclonal Protein Study, Random, Urine

Clinical Information:
Urine proteins can be grouped into 5 fractions by protein electrophoresis: Albumin, Alpha-1, Alpha-2, Beta-globulin, Gamma-globulin. The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The use of a random urine specimen is sufficient for identifying the presence or absence of a monoclonal immunoglobulin, but a 24 hour specimen is preferred for quantitating and monitoring the abnormality. See An Expanded Algorithm for the Laboratory Evaluation of Suspected Multiple Myeloma in Special Instructions and the Laboratory Approach to the Diagnosis of Amyloidosis algorithm in Special Instructions. Also see Diagnosis and Monitoring of Multiple Myeloma in Publications.

Useful For:
Diagnosing monoclonal gammopathies

Interpretation:
A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration is followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin free light chains as well as heavy chain fragments may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light-chain M-spike of >1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hrs) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) or light-chain deposition disease (LCDD). Because patients with AL or LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also performed.

Reference Values:
ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as a percent of the total protein:
- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin
- Gamma-globulin
No reference values apply to random urine.
Monoclonal Protein Study, Serum

Clinical Information: Serum proteins can be grouped into 5 fractions by protein electrophoresis:
- Albumin, which represents almost two-thirds of the total serum protein
- Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein
- Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin
- Beta, composed primarily of transferrin and complement C3
- Gamma, composed primarily of immunoglobulins (Ig)

The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases. The following algorithms are available in Special Instructions:
- Laboratory Approach to the Diagnosis of Amyloidosis
- Laboratory Screening Tests for Suspected Multiple Myeloma

Also see Diagnosis and Monitoring of Multiple Myeloma in Publications.

Useful For: Diagnosis of monoclonal gammopathies, when used in conjunction with urine monoclonal studies

Monitoring patients with monoclonal gammopathies

Protein electrophoresis alone is not considered an adequate screen for monoclonal gammopathies

Interpretation:

Monoclonal Gammopathies: A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin (Ig) heavy chain and/or light chain.

- A monoclonal IgG or IgA >3 g/dL is consistent with multiple myeloma (MM).
- A monoclonal IgG or IgA <3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. 
- A monoclonal IgM >3 g/dL is consistent with macroglobulinemia.

- The initial identification of a serum M-spike >1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. 
- The initial identification of an IgM, IgA, or IgG M-spike >4 g/dL, >5 g/dL, and >6 g/dL respectively, should be followed by VISCS / Viscosity, Serum. 
- After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is >0.5 g/dL is considered a significant change.

- Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and PEL should not be used to screen for the disorder.

MPSS / Monoclonal Protein Study, Serum, which includes IF, should be done to screen if the clinical suspicion is high. Other Abnormal PEL Findings: A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease.

- A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. 
- A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. 
- In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoaalphabuminemia), the affected fraction is faint or absent. 
- An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:

PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS

Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.
Reference values have not been established for patients that are <16 years of age.

IMMUNOFIXATION

No monoclonal protein detected


Monospecific Direct Coombs C3, Blood

Clinical Information: Complement, in conjunction with IgM antibody, may be present on patient or donor (transfused) RBCs and may cause hemolysis. The antibody may be directed against self-antigens (autoimmune hemolysis), maternal antigens (hemolytic disease of the newborn), donor antigens (eg, alloimmune transfusion reaction), or drugs. The presence of in vivo coating of RBC with complement can be demonstrated by the direct antiglobulin (Coombs) test.

Useful For: Detecting complement bound to RBC Investigation of hemolytic anemia

Interpretation: The presence or absence of red cell-bound complement is used in conjunction with other testing and clinical data to aid in the characterization of hemolysis as immune-mediated. Possible causes include autoimmune hemolytic anemia, drug-induced hemolysis, hemolytic disease of the newborn, and alloimmune reactions to recently transfused RBC.

Reference Values:
Negative
If positive, reaction is graded (positive 1+ to 4+).

Monospecific Direct Coombs IgG, Blood

Clinical Information: IgG antibody may be present on patient or donor (transfused) RBCs and may cause hemolysis. The antibodies may be directed against self-antigens (autoimmune hemolysis), maternal antigens (hemolytic disease of the newborn), donor antigens (eg, alloimmune transfusion reaction), or drugs. The presence of in vivo coating of RBC with IgG can be demonstrated by the direct antiglobulin (Coombs) test.

Useful For: Detecting antibodies bound to RBC Investigation of hemolytic anemia

Interpretation: The presence or absence of IgG is used in conjunction with other testing and clinical data to aid in the characterization of Hemolysis as immune-mediated. Possible causes include autoimmune hemolytic anemia, drug-induced hemolysis, hemolytic disease of the newborn, and alloimmune reactions to recently transfused RBC.

Reference Values:
Negative
If positive, reaction is graded (positive 1+ to 4+).
**FMORS 75144**

**Morphine Confirmation, Serum**

**Reference Values:**
- Report Limit: 1 ng/mL
- Reference Range: 21 ± 65 ng/mL

**SPSM 9184**

**Morphology Evaluation (Special Smear)**

**Clinical Information:** Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count/special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.

**Useful For:** Detecting disease states or syndromes of the white blood cells, red blood cells, or platelet cell lines of a patient's peripheral blood

**Interpretation:** The laboratory will provide an interpretive report of percentage of white cells and, if appropriate, evaluation of white cells, red cells, and platelets.

**Reference Values:**
An interpretive report will be provided.


**MSPP 82845**

**Mosquito Species, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT
Moth, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Motilin, Plasma or Serum

Clinical Information: Motilin is a 22 amino acid peptide produced primarily by the enterochromaffin cells (EC2 or M cells) in the intestine, duodenum and the jejunum. It is absent from the stomach and colon. Motilin accelerates gastric emptying and colonic motor activity. Motilin also stimulates the feeding response. It has no structural similarities with other gastrointestinal peptides. Motilin secretion can be stimulated by acid and a fat-rich meal. Motilin can increase the secretion of pepsin and causes increased intra-gastric pressure. Motilin also stimulates lower esophageal sphincter contraction. Motilin levels are suppressed by Calcitonin. Motilin has a short half-life of approximately five minutes.

Reference Values:
Up to 446 pg/mL

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

Motor Neuropathy Panel

Reference Values:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Value Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 30 days</td>
<td>0 – 24 mg/dL</td>
</tr>
<tr>
<td>9 – 11 months</td>
<td>39 – 142 mg/dL</td>
</tr>
<tr>
<td>1 year</td>
<td>41 – 164 mg/dL</td>
</tr>
<tr>
<td>2 years</td>
<td>46 – 160 mg/dL</td>
</tr>
<tr>
<td>3 years</td>
<td>45 – 190 mg/dL</td>
</tr>
<tr>
<td>4 years</td>
<td>41 – 186 mg/dL</td>
</tr>
<tr>
<td>5 years</td>
<td>46 – 197 mg/dL</td>
</tr>
<tr>
<td>6 years</td>
<td>49 – 230 mg/dL</td>
</tr>
<tr>
<td>7 – 8 months</td>
<td>68 – 408 mg/dL</td>
</tr>
<tr>
<td>10 years and older</td>
<td>68 – 1362 mg/dL</td>
</tr>
</tbody>
</table>

Immunoglobulin G

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Value Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 30 days</td>
<td>611 – 1542 mg/dL</td>
</tr>
<tr>
<td>9 – 11 months</td>
<td>16 – 83 mg/dL</td>
</tr>
<tr>
<td>1 year</td>
<td>14 – 105 mg/dL</td>
</tr>
<tr>
<td>2 years</td>
<td>14 – 122 mg/dL</td>
</tr>
<tr>
<td>3 years</td>
<td>22 – 157 mg/dL</td>
</tr>
<tr>
<td>4 years</td>
<td>25 – 152 mg/dL</td>
</tr>
<tr>
<td>5 years</td>
<td>33 – 300 mg/dL</td>
</tr>
<tr>
<td>6 years</td>
<td>45 – 234 mg/dL</td>
</tr>
<tr>
<td>7 – 8 months</td>
<td>80 – 408 mg/dL</td>
</tr>
<tr>
<td>10 years and older</td>
<td>80 – 1362 mg/dL</td>
</tr>
</tbody>
</table>

Immunoglobulin M

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Value Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 30 days</td>
<td>0 – 24 mg/dL</td>
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<tr>
<td>9 – 11 months</td>
<td>19 – 83 mg/dL</td>
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<tr>
<td>1 year</td>
<td>23 – 85 mg/dL</td>
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<tr>
<td>2 years</td>
<td>23 – 96 mg/dL</td>
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<tr>
<td>3 years</td>
<td>31 – 103 mg/dL</td>
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<tr>
<td>4 years</td>
<td>33 – 97 mg/dL</td>
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<tr>
<td>5 years</td>
<td>33 – 97 mg/dL</td>
</tr>
<tr>
<td>6 years</td>
<td>33 – 97 mg/dL</td>
</tr>
<tr>
<td>7 – 8 months</td>
<td>33 – 97 mg/dL</td>
</tr>
<tr>
<td>10 years and older</td>
<td>33 – 97 mg/dL</td>
</tr>
</tbody>
</table>
7–8 months: 32–120 mg/dL 10 years and older: 35–263 mg/dL Myelin Associated Glycoprotein (MAG) Antibody, IgM
Less than 1000 TU An elevated IgM antibody concentration greater than 999 TU against myelin-associated glycoprotein (MAG) suggests active demyelination in peripheral neuropathy. A normal concentration (less than 999 TU) generally rules out an anti-MAG antibody-associated peripheral neuropathy. TU = Titer Units
Sulfate-3 Glucuronyl Paragloboside (SGPG) Antibody, IgM
Less than 1.00 IV
The majority of sulfate-3-glucuronyl paragloboside (SGPG) IgM-positive sera will show reactivity against MAG. Patients who are SGPG IgM positive and MAG IgM negative may have multi-focal motor neuropathy with conduction block.

Mountain Cedar, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**MOUS 82707**

**Mouse Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<tbody>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**MOSP 82792**

**Mouse Serum Protein, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>2</td>
<td>0.70-3.49</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**MOUP 82795**

**Mouse Urine Protein, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm...
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


---

**MPL Exon 10 Mutation Detection, Blood**

**Clinical Information:** DNA sequence mutations in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocythemia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase and the most common MPL mutations are single base pair substitutions at codon 515. These mutations have been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 mutations have been identified in PMF and ET to date, and mutations outside of exon 10 have not yet been reported. The vast majority of MPL mutations have been found in specimens testing negative for the most common mutation identified in myeloproliferative neoplasms, JAK2 V716F, although a small number of cases with both types of mutations have been reported. MPL mutations have not been identified in patients with polycythemia vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL mutations can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm

**Interpretation:** The results will be reported as 1 of 2 states: -Negative for MPL exon 10 mutation -Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:** An interpretive report will be provided.

MPLM 60024

MPL Exon 10 Mutation Detection, Bone Marrow

Clinical Information: DNA sequence mutations in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocytopenia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase and the most common MPL mutations are single base pair substitutions at codon 515. These mutations have been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 mutations have been identified in PMF and ET to date, and mutations outside of exon 10 have not yet been reported. The vast majority of MPL mutations have been found in specimens testing negative for the most common mutation identified in myeloproliferative neoplasms, JAK2 V716F, although a small number of cases with both types of mutations have been reported. MPL mutations have not been identified in patients with polycythemia vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL mutations can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

Useful For: Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm

Interpretation: The results will be reported as 1 of 2 states: -Negative for MPL exon 10 mutation -Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References:

MPLR 36682

MPL Exon 10 Mutation Detection, Reflex

Reference Values:
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

MPLVA 61746

MPL Exon 10 Mutation Detection, Varies

Clinical Information: DNA sequence mutations in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocytopenia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase and the most common MPL mutations are single base pair substitutions at codon 515. These mutations have been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 mutations have been identified in PMF and ET to date, and mutations outside of exon 10 have not yet been reported. The vast majority of MPL mutations have been found in specimens testing negative for the most common mutation identified in myeloproliferative neoplasms, JAK2 V716F, although a small number of cases with both types of mutations have been reported. MPL mutations have not been identified in patients with polycythemia...
vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL mutations can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm

**Interpretation:** The results will be reported as 1 of 2 states: -Negative for MPL exon 10 mutation -Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.


**MSH2I**
**MSH-2, Immunostain (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MSH6I**
**MSH-6, Immunostain (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MSH2Z**
**MSH2 Gene, Full Gene Analysis**
**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch...
syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MSH2 and MSH6 are more likely to have a germline mutation in the MSH2 gene.

**Useful For:** Determining whether absence of MSH2 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer Identification of familial MSH2 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MSH6 Gene, Full Gene Analysis**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPPC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MSH6 are more likely to have a germline mutation in the MSH6 gene.

**Useful For:** Determining whether absence of MSH6 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual Establishing a diagnosis of Lynch syndrome...
syndrome/hereditary nonpolyposis colorectal cancer

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MTBVP**

**60270**

**Mtbg PZA Confirmation, pncA Sequencing (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

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**MCIVP**

**35482**

**Mucolipidosis IV, Mutation Analysis, IVS3(-2)A->G and del6.4kb**

**Clinical Information:** Mucolipidosis IV is a lysosomal storage disease characterized by mental retardation, hypotonia, corneal clouding, and retinal degeneration. Mutations in the MCOLN1 gene are responsible for the clinical manifestations of mucolipidosis IV. The carrier rate in the Ashkenazi Jewish population is 1 in 127. Two mutations in the MCOLN1 gene account for the majority of mutations in the Ashkenazi Jewish population: IVS3(-2)A->G and del6.4kb. The detection rate for these 2 mutations is approximately 95%.

**Useful For:** Carrier testing for mucolipidosis IV in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of mucolipidosis IV for at-risk pregnancies Confirmation of suspected clinical diagnosis of mucolipidosis IV in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MPSSC**

**84464**

**Mucopolysaccharides (MPS) Screen, Urine**

**Clinical Information:** The mucopolysaccharidoses (MPSs) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPSs. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in
I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. MPSs are autosomal recessive disorders with the exception of MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary, and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood. A diagnostic workup for individuals with suspected MPS should begin with test MPSSC Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total GAGs and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the qualitative analysis of their relative amounts of excretion. However, an abnormal MPS analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) and/or molecular analysis. After a specific diagnosis has been established, MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine, which does not include the analysis of the specific sulfates, can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy. However, some clinicians will opt to perform the MPS screen, which allows for monitoring of not only the total amount of GAGs, but also the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment. Table: Enzyme Defects and Excretion Products of Mucopolysaccharidoses Disorder Alias Enzyme Deficiency (Mayo Medical Laboratories’ Test, if applicable) Sulfate(s) Excreted MPS I Hurler/Scheie alpha-L-iduronidase (IDST) DS/HS MPS II Hunter Iduronate 2-sulfatase DS/HS MPS III A Sanfilippo A Heparan N-sulfatase HS MPS III B Sanfilippo B N-acetyl-alpha-D-glucosaminidase (ANAT, ANAS) HS MPS III C Sanfilippo C Acetyl-CoA:alpha-glucosaminide N-acetyltransferase HS MPS III D Sanfilippo D N-acetylglucosamine-6-sulfatase HS MPS IV A Morquio A Galactosamine-6-sulfatase (G6ST) KS/C6S MPS IV B Morquio B beta-galactosidase (B GaT, B Ga) KS MPS VI Maroteaux-Lamy Arylsulfatase B (ARSB) DS MPS VII Sly beta-glucuronidase (BGLR) DS/HS/C6S MPS IX Hyaluronidase deficiency Hyaluronidase None KEY: C6S, chondroitin 6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate MPS I (Hurler/Scheie syndrome) is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized into 3 phenotypes: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme.
Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals. MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAGs are normal in MPS IX. Multiple sulfatase deficiency (MSD) is an autosomal recessive disorder caused by mutations in the sulfatase-modifying factor-1 gene (SUMF1). Sulfatases undergo a common process that allows for normal expression of enzyme activity. Mutations in SUMF1 impair that process, thereby resulting in decreased activity of all known sulfatase enzymes. Individuals with MSD have a complex clinical presentation encompassing features of each of the distinct enzyme deficiencies, including iduronate 2-sulfatase (MPS II), N-acetylgalactosamine-6-sulfate sulfatase (MPS IVA), arylsulfatase B (MPS VI), and arylsulfatase A (metachromatic leukodystrophy), steroid sulfatase (X-linked ichthyosis) and arylsulfatase F (chondrodysplasia punctata). MSD is extremely rare, affecting approximately 1 in 1,400,000 individuals.

Useful For: Preferred screening test for mucopolysaccharidoses

Interpretation: An abnormally elevated excretion of glycosaminoglycans is characteristic of mucopolysaccharidoses. The pattern of sulfates obtained by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is usually characteristic of the enzyme deficiency. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test).

Reference Values:
MPS, QUANTITATIVE
0-4 months: < or =53.0 mg/mmol creatinine
5-18 months: < or =31.0 mg/mmol creatinine
19 months-2 years: < or =24.0 mg/mmol creatinine
3-5 years: < or =16.0 mg/mmol creatinine
6-10 years: < or =12.0 mg/mmol creatinine
11-14 years: < or =10.0 mg/mmol creatinine
>14 years: < or =6.5 mg/mmol creatinine
MPS, QUALITATIVE
An interpretive report will be provided.


Mucopolysaccharides (MPS), Quantitative, Urine

Clinical Information: The mucopolysaccharides (MPSs) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPSs. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. MPSs are autosomal recessive disorders with the exception of MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary, and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood. Additional information regarding individual disorders can be found under test MPSSC / Mucopolysaccharides (MPS) Screen, Urine. A diagnostic workup for individuals with suspected MPS should begin with MPSSC / Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total GAGs and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Interpretation is based upon pattern recognition of the specific sulfate(s) detected by MS/MS and the qualitative analysis of their relative amounts of excretion. However, an abnormal MPS analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) and/or molecular analysis. After a specific diagnosis has been established, MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine, which does not include the analysis of the specific sulfates, can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy. However, some clinicians will opt to perform the MPS screen, which allows for monitoring of not only the total amount of GAGs, but also the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment. Table: Enzyme Defects and Excretion Products of Mucopolysaccaridoses Disorder Alias Enzyme Deficiency (Mayo Medical Laboratories’ Test, if applicable) Sulfate(s) Excreted MPS I Hurler/Scheie alpha-L-iduronidase (IDST) DS/HS MPS II Hunter Iduronate 2-sulfatase DS/HS MPS III A Sanfilippo A Heparan N-sulfatase HS MPS III B Sanfilippo B N-acetyl-alpha-D-gluacosaminidase (ANAT, ANAS) HS MPS III C Sanfilippo C Acetyl-CoA:alpha-glucosaminide N-acetyltransferase HS MPS III D Sanfilippo D N-acetylglucosamine-6-sulfatase HS MPS IV A Morquio A Galactosamine-6-sulfatase (G6ST) KS/C6S MPS IV B Morquio B beta-galactosidase (B GaT, B GA) KS MPS VI Maroteaux-Lamy Arylsulfatase B (ARSB) DS MPS VII Sly beta-glucuronidase (BGLR) DS/HS/C6S MPS IX Hyaluronidase deficiency Hyaluronidase None KEY: C6S, chondroitin 6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate MPS I (Hurler/Scheie syndrome) is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized into 3 phenotypes: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and
attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IV A (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IV B (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals. MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAGs are normal in MPS IX. Multiple sulfatase deficiency (MSD) is an autosomal recessive disorder caused by mutations in the sulfatase-modifying factor-1 gene (SUMF1). Sulfatases undergo a common process that allows for normal expression of enzyme activity. Mutations in SUMF1 impair that process, thereby resulting in decreased activity of all known sulfatase enzymes. Individuals with MSD have a complex clinical presentation encompassing features of each of
the distinct enzyme deficiencies, including iduronate 2-sulfatase (MPS II), N-acetylgalactosamine-6-sulfate sulfatase (MPS IVA), arylsulfatase B (MPS VI), and arylsulfatase A (metachromatic leukodystrophy), steroid sulfatase (X-linked ichthyosis) and arylsulfatase F (chondrodysplasia punctata). MSD is extremely rare, affecting approximately 1 in 1,400,000 individuals.

Useful For: Monitoring patients with mucopolysaccharidosis who have had bone marrow transplants or are receiving enzyme therapy. Note: The preferred test to screen for mucopolysaccharides (MPS) is MPSSC / Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total glycosaminoglycans and qualitative liquid chromatography-tandem mass spectrometry analysis of the specific sulfates.

Interpretation: An abnormally elevated excretion of glycosaminoglycan (GAG) is characteristic of mucopolysaccharidoses. GAG levels may normalize or remain elevated in patients who have undergone bone marrow transplants or are receiving enzyme replacement therapy.

Reference Values:
0-4 months: < or =53.0 mg/mmol creatinine
5-18 months: < or =31.0 mg/mmol creatinine
19 months-2 years: < or =24.0 mg/mmol creatinine
3-5 years: < or =16.0 mg/mmol creatinine
6-10 years: < or =12.0 mg/mmol creatinine
11-14 years: < or =10.0 mg/mmol creatinine
>14 years: < or =6.5 mg/mmol creatinine


Mucopolysaccharidosis IIIA, Full Gene Analysis
Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIIA (MPS-IIIa, or Sanfilippo syndrome A, is caused by mutations in the SGSH gene and is characterized by reduced or absent activity of the sulfamidase enzyme. This test screens for mutations in all 8 exons of the SGSH gene. Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

Useful For: Identifying mutations within the SGSH gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIA Carrier testing, when there is a family history of mucopolysaccharidosis type IIIA, but disease-causing mutations have not been previously identified.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


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Mucopolysaccharidosis IIIIB, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIIB (MPS-IIIB), or Sanfilippo syndrome B, is caused by mutations in the NAGLU gene and is characterized by reduced or absent activity of the N-acetyl-alpha-D-glucosaminidase. This test screens for mutations in all 6 exons of the NAGLU gene. Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

Useful For: Identifying mutations within the NAGLU gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIB Carrier testing, when there is a family history of mucopolysaccharidosis type IIIB, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Mucopolysaccharidosis IIID, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIID (MPS-IIID), or Sanfilippo syndrome D, is caused by mutations in the GNS gene and is characterized by reduced or absent activity of the N-acetylglucosamine-6-sulfatase enzyme. This test screens for mutations in all 14 exons of the GNS gene. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

Useful For: Identifying mutations within the GNS gene Confirmation of a diagnosis of mucopolysaccharidosis type IIID Carrier testing when there is a family history of mucopolysaccharidosis type IIID, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
MPS6Z 35507

**Mucopolysaccharidosis VI, Full Gene Analysis**

**Clinical Information:** Mucopolysaccharidosis type VI (MPS-VI), also known as Maroteaux-Lamy syndrome, is an autosomal recessive condition that is caused by mutations in the ARSB gene and is characterized by reduced or absent activity of the arylsulfatase B enzyme. This test screens for mutations in all 8 exons of the ARSB gene. The clinical features and severity of symptoms of Maroteaux-Lamy are widely variable. Typically it is characterized by short stature, dysostosis multiplex, facial dysmorphism, stiff joints, hepatosplenomegaly, corneal clouding, cardiac defects, and usually normal intelligence. With a rapidly progressing form of MPS-VI, onset occurs before 2 to 3 years of age with death typically occurring in the second to third decade. With a slowly progressing form of MPS-VI, a diagnosis usually occurs after 5 years of age but may not occur until the second or third decade. The recommended first-tier test for MPS-VI is biochemical testing that measures arylsulfatase B enzyme activity in fibroblasts (ARSB / Arylsulfatase B, Fibroblasts). Individuals with decreased or absent enzyme activity are more likely to have 2 identifiable mutations in the ARSB gene by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers.

**Useful For:** Identifying mutations within the ARSB gene Confirmation of a diagnosis of mucopolysaccharidosis type VI Carrier testing, when there is a family history of mucopolysaccharidosis type VI, but disease-causing mutations have not been previously identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


MUC 82675

**Mucor, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Mugwort, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Mulberry, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
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</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
<td></td>
</tr>
</tbody>
</table>
MSP2

**Multiple Sclerosis (MS) Profile**

**Clinical Information:** Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease characterized by visual, motor, and sensory disturbances. The diagnosis of MS is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the cerebrospinal fluid (CSF) IgG index and CSF oligoclonal band detection.

**Useful For:** Diagnosing multiple sclerosis, especially helpful in patients with equivocal clinical or radiological findings

**Interpretation:** Oligoclonal banding (OCB): > or =4 cerebrospinal fluid (CSF)-specific bands are consistent with multiple sclerosis (MS). CSF IgG index: >0.85 is consistent with MS. Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of MS patients. If both tests are performed, at least 1 of the tests has been reported to be positive in >90% of multiple sclerosis patients. A newer methodology for OCB detection, isoelectric focusing, is utilized in this test and has been reported to be more sensitive (90%-95%). The presence of OCB or elevated CSF IgG index is unrelated to disease activity.

**Reference Values:**

<table>
<thead>
<tr>
<th>OLIGOCLONAL BANDS</th>
<th>&lt;4 bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF INDEX</td>
<td></td>
</tr>
<tr>
<td>CSF IgG index: 0.00-0.85</td>
<td></td>
</tr>
<tr>
<td>CSF IgG: 0.0-8.1 mg/dL</td>
<td></td>
</tr>
<tr>
<td>CSF albumin: 0.0-27.0 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Serum IgG</td>
<td></td>
</tr>
<tr>
<td>0-4 months: 100-334 mg/dL</td>
<td></td>
</tr>
<tr>
<td>5-8 months: 164-588 mg/dL</td>
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<td>9-14 months: 246-904 mg/dL</td>
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<tr>
<td>15-23 months: 313-1,170 mg/dL</td>
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<tr>
<td>2-3 years: 295-1,156 mg/dL</td>
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<td>4-6 years: 386-1,470 mg/dL</td>
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<td>7-9 years: 462-1,682 mg/dL</td>
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<td>10-12 years: 503-1,719 mg/dL</td>
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<td>13-15 years: 509-1,580 mg/dL</td>
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<tr>
<td>16-17 years: 487-1,327 mg/dL</td>
<td></td>
</tr>
<tr>
<td>&gt; or =18 years: 767-1,590 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Serum albumin: 3,200-4,800 mg/dL</td>
<td></td>
</tr>
<tr>
<td>CSF IgG/albumin: 0.0-0.21</td>
<td></td>
</tr>
<tr>
<td>Serum IgG/albumin: 0.00-0.40</td>
<td></td>
</tr>
<tr>
<td>CSF IgG synthesis rate: 0-12 mg/24 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical References:**

SUMFZ

**Multiple Sulfatase Deficiency, Full Gene Analysis**

**Clinical Information:** Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal storage disorder (LSD) caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1
encodes for a formylglycine-generating enzyme (FGE) that performs a critical posttranslational modification of the catalytic residue necessary for activation of all human sulfatases. MSD is often confused for a single sulfatase deficiency because it is characterized by deficiency of all known sulfatases, which results in tissue accumulation of sulfatides, sulfated glycosaminoglycans, sphingolipids, and steroid sulfates. Indeed, the clinical phenotype encompasses symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy (MLD), the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Age of onset and clinical severity are variable and correspond with the level of residual FGE enzyme activity. A severe neonatal form of MSD closely overlaps the clinical presentation of the mucopolysaccharidoses but it is often fatal within 1 year. Late-infantile MSD (onset 0-2 years) accounts for most cases and is characterized by a clinical presentation similar to MLD. Patients show progressive cognitive and motor impairment as well as skeletal changes. More rarely, MSD presents in late childhood (juvenile-onset) with more mild symptoms and slower progression. Patients with late-infantile or juvenile-onset MSD may have less severe sulfatase deficiency. Patients with a clinical suspicion of MLD, a mucopolysaccharidosis, X-linked ichthyosis, or chondrodysplasia should be investigated for possible FGE deficiency. Urine sulfatide analysis is the recommended first tier biochemical test (CTSA / Ceramide Trihexoside/Sulfatide Accumulation in Urine Sediment, Urine). If positive, iduronate sulfatase and arylsulfatase A and B enzyme levels should be assayed and are typically decreased in patients with MSD. While enzyme replacement therapy has been used to treat a subset of single LSD, its effectiveness is not well established for patients with MSD. Therefore, confirmation or exclusion of a diagnosis of MSD has important implications for patient management as well as prognosis.

**Useful For:** Confirmation of multiple sulfatase deficiency for patients with clinical features
Identification of SUMF1 mutation to allow for genetic testing in family members

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CMUMP 81435**

**Mumps Virus Antibodies, IgG and IgM (Separate Determinations), Spinal Fluid**

**Clinical Information:** There is only 1 serotype of mumps virus that infects humans. Mumps has been recognized since antiquity by virtue of the parotitis that is often a striking clinical feature of the disease. Generally, a trivial childhood illness, the varied presentation of mumps reflects the widespread invasion of visceral organs and central nervous system that commonly follows infection with mumps virus.

**Useful For:** Aiding in the diagnosis of central nervous system infection by mumps virus

**Interpretation:** Normals: IgG: <1:5 IgM: <1:10 Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

**Reference Values:**

---
IgG: <1:5  
IgM: <1:10


**FMUMM**  
91456  
**Mumps Virus Antibody, (IgM)**

**Reference Values:**
Reference Range: <1:20

Interpretive Criteria:
<1:20 Antibody not detected
>or= 1:20 Antibody detected

The presence of IgM antibody to mumps typically indicates recent or current mumps infection; however, false positive results may occur due to antibody crossreactivity to parainfluenza virus.

**MPPG**  
34947  
**Mumps Virus Antibody, IgG, Serum**

**Clinical Information:** The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus (RSV), and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2 week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(1,2) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens.

**Useful For:** Determination of postimmunization immune response of individuals to the mumps vaccine  
Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

**Interpretation:** Positive: The presence of detectable IgG-class antibodies indicates prior exposure to the mumps virus through infection or immunization. Individuals testing positive are considered immune to mumps virus. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies suggests no prior exposure to the mumps virus or the lack of a specific immune response to immunization.

**Reference Values:**
Vaccinated: Positive (> or =1.1 AI)  
Unvaccinated: Negative (< or =0.8 AI)

**Clinical References:**  

Current as of July 8, 2016 11:28 am CDT  
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  
Page 1373
Mumps Virus Antibody, IgM and IgG (Separate Determinations), Serum

Clinical Information: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.1,2 Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.1 Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens.

Useful For: Laboratory diagnosis of mumps virus infection Determination of postimmunization immune response of individuals to the mumps vaccine Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

Interpretation: A positive IgG result coupled with a positive IgM result suggests recent infection with mumps virus. This result should not be used alone to diagnose mumps infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with mumps virus. These individuals are considered to have protective immunity to reinfection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to mumps virus and nonimmunity. However, a negative result does not rule-out mumps infection or response to vaccination. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early mumps infection or within a week following vaccination should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

Reference Values:
IgM
Negative (reported as positive, equivocal, or negative)
Index value 0.00-0.79=negative

IgG
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)

complications include pancreatitis (<5% of cases) and central nervous system disease (meningitis/encephalitis) that occur rarely (about 1 in 6,000 cases of mumps). Widespread routine immunization of infants with attenuated mumps virus has changed the epidemiology of this virus infection. Since 1989, there has been a steady decline in reported mumps cases, with an average of 265 cases each year since 2001. However, a recent outbreak of mumps in 2006 reemphasized that this virus continued to persist in the population, and laboratory testing may be needed in clinically compatible situations. The laboratory diagnosis of mumps is typically accomplished by detection of antibody to mumps virus. However, due to the limitations of serology (eg, inadequate sensitivity and specificity), additional laboratory testing including virus isolation or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens should be considered in clinically compatible situations.

**Useful For:** Laboratory diagnosis of mumps virus infection

**Interpretation:** Positive: presence of IgM-class antibodies to mumps virus may support a clinical diagnosis of recent/acute phase infection with this virus. Negative: absence of IgM-class antibodies to mumps virus suggests lack of acute phase infection with mumps virus. However, serology may be negative in early disease, and results should be interpreted in the context of clinical findings.

**Reference Values:**

- Negative (reported as positive, equivocal, or negative)
  - Index value 0.00-0.79 = negative

**Clinical References:**

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**FMTAG 57260**

**Murine Typhus Antibodies, IgG**

**Reference Values:**

**Reference Interval:**
- Negative <1:64
- Present or Past 1:64
- Recent/Active >1:64

**Clinical References:**

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**MBCT 37419**

**Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks**

**Clinical Information:** In our consultative practice, we strive to bring the customer the highest quality of diagnostic neuromuscular pathology, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

**Useful For:** Obtaining a rapid, expert opinion on muscle biopsy specimens

**Interpretation:** Results are reported in a formal neuromuscular pathology report that includes an interpretive comment, if necessary. The formal pathology report is faxed or sent by mail according to the preference of the referring institution.

**Reference Values:**

An interpretive report will be provided.


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**MCOS 64343**

**Muscle Consult, Outside Slide (Bill Only)**
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**MCRV**

**Muscle Consult, w/Complex Rvw of Hx (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**MCSP**

**Muscle Consult, w/Slide Prep (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**MCPRO**

**Muscle Consult, w/USS Prof (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**MPCT**

**Muscle Pathology Consultation**

**Clinical Information:** In our consultative practice, we strive to bring the customer the highest quality of diagnostic neuromuscular pathology, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

**Useful For:** Obtaining a rapid, expert opinion on unprocessed muscle specimens

**Interpretation:** Results are reported in a formal neuromuscular pathology report that includes an interpretive comment, if necessary. The formal pathology report is faxed or sent by mail according to the preference of the referring institution.

**Reference Values:**
An interpretive report will be provided.


**MCL4**

**Muscle, Level IV Consult (Bill Only)**
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**MUSK 64277**

**Muscle-Specific Kinase (MuSK) Autoantibody, Serum**

**Clinical Information:** Fatigable weakness due to impaired synaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). The diagnosis is made by clinical and electromyographic criteria. Positive autoimmune serology must be interpreted in the clinical and electrophysiological context and response to anticholinesterase medication. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic acetylcholine receptor or its interacting proteins). (1) Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (71% muscle acetylcholine receptor: AChR binding). (2) Mayo Clinic's first-line serological evaluation detects muscle AChR antibody in 92% of nonimmunosuppressed patients with generalized weakness due to MG. Muscle-specific kinase (MuSK) antibody is detectable in more than one-third of those seronegative for muscle AChR antibody (less than 4% of all patients). (3) Physiologically, MuSK is involved in integrating and stabilizing AChR clusters in the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Antibodies to LRP4 itself have been described in rare patients. (1) Six percent of nonimmunosuppressed patients with generalized MG lack demonstrable AChR or MuSK antibodies (double seronegative). Other rare autoantibodies no doubt remain to be discovered in such cases. However, as in autoimmune AChR MG and MuSK MG, testing for common organ-specific and nonorgan-specific autoantibodies is a valuable ancillary investigation in evaluating seronegative acquired generalized MG. General serological testing, coupled with family or personal history, will disclose autoimmune phenomena in 77% of those cases. (3) These disorders may include thyroid disease, type 1 diabetes, vitiligo, premature greying, rheumatoid arthritis, or lupus. Testing may also reveal antinuclear antibodies, glutamic acid decarboxylase (GAD65) antibodies, thyroperoxidase/thyroglobulin antibodies, or gastric parietal cell antibodies. (3) Objective improvement in strength following a therapeutic trial of plasmapheresis or intravenous immune globulin would justify consideration of long-term immunosuppression. Females are generally affected by autoimmune MuSK MG more often than males. Onset can occur at any age (pediatric to elderly). Patients may derive limited benefit from anticholinesterase medication. The thymus is normal, and patients are generally not benefited by thymectomy. Antibody-lowering therapies are effective. Bulbar, facial, and respiratory weakness are prominent, and crises are common. (1,4)

**Useful For:** Diagnosis of autoimmune muscle-specific kinase (MuSK) myasthenia gravis Second-order test to aid in the diagnosis of autoimmune myasthenia gravis when first-line serologic tests are negative Establishing a quantitative baseline value for MuSK antibodies that allows comparison with future levels if weakness is worsening

**Interpretation:** A positive result, in the appropriate clinical context, confirms the diagnosis of autoimmune muscle-specific kinase myasthenia gravis. Seropositivity justifies consideration of immunotherapy.

**Reference Values:**
< or =0.02 nmol/L

Mushroom IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Mushroom, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
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<td>Strongly positive</td>
</tr>
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Reference values apply to all ages.

Mustard Food IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Mustard, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages</td>
</tr>
</tbody>
</table>

Clinical References: Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
MVista Blastomyces Quantitative Antigen

Interpretation:

Reference Values:
Reference Value: None Detected
Results reported as ng/mL in 0.2 - 14.7 ng/mL range
Results above the limit of detection but below 0.2 ng/mL are reported as 'Positive, Below the Limit of Quantification'
Results above 14.7 ng/mL are reported as 'Positive, Above the Limit of Quantification'

MVista Coccidioides Antigen EIA

Reference Values:
Reference interval: None Detected
Results reported as ng/mL in 0.07 - 8.2 ng/mL range
Results above 8.2 ng/mL are reported as 'Positive, Above the Limit of Quantification'

MVista Histoplasma Ag Quantitative EIA

Reference Values:
Reference interval: None Detected
Results reported as ng/mL in 0.4 â€“ 19 ng/mL range
Results above the limit of detection but below 0.4 ng/mL are reported as 'Positive, Below the Limit of Quantification'.
Results above 19.0 ng/mL are reported as 'Positive, Above the Limit of Quantification'.

MVista Histoplasma Ag Quantitative, Serum

Reference Values:
Reference interval: None Detected
Results reported as ng/mL in 0.4 â€“ 19.0 ng/mL range
Results above the limit of detection, but below 0.4 ng/mL are reported as 'Positive, Below the Limit of Quantitation'.
Results above 19.0 ng/mL are reported as 'Positive, Above the Limit of Quantitation'.

MVista Histoplasma Ag Quantitative, Spinal Fluid

Reference Values:
Reference interval: None Detected
Results reported as ng/mL in 0.4 â€“ 19 ng/mL range
Results above the limit of detection by below 0.4 ng/mL are reported as 'Positive, Below the Limit of Quantification'.

Results above 19.0 ng/mL are reported as 'Positive, Above the Limit of Quantification'.

**Myasthenia Gravis (MG) Evaluation, Adult**

**Clinical Information:** Myasthenia gravis (MG) is an acquired disorder of neuromuscular transmission caused by the binding of pathogenic autoantibodies to muscle's postsynaptic nicotinic acetylcholine receptor (AChR). In a small minority of patients the pathogenic antibody is directed at the muscle-specific receptor tyrosine kinase (MuSK) antigen. The ensuing weakness in both cases reflects a critical loss of the AChR channel protein, which is required to activate the muscle action potential. MG affects children (see MGEP / Myasthenia Gravis [MG] Evaluation, Pediatric) as well as adults. In adults with MG there is at least a 20% occurrence of thymoma or other neoplasm. Neoplasms are an endogenous source of the antigens driving production of autoantibodies. Autoimmune serology is indispensable for initial evaluation and monitoring of patients with acquired disorders of neuromuscular transmission. The neurological diagnosis depends on the clinical context and electromyographic findings, and is confirmed more readily by the individual patient’s serological profile than by any single test. Not all of the antibodies detected in this profile impair neuromuscular transmission (eg, antibodies directed at cytoplasmic epitopes accessible on solubilized AChR, or sarcomeric proteins that constitute the striational antigens). See Myasthenia Gravis: Adult Diagnostic Algorithm in Special Instructions.

**Useful For:** Initial evaluation of patients aged 20 or older with symptoms and signs of acquired myasthenia gravis (MG) Bone marrow transplant recipients with suspected graft-versus-host disease, particularly if weakness has appeared Confirming that a recently acquired neurological disorder has an autoimmune basis (eg, MG) Providing a quantitative baseline for future comparisons in monitoring a patient's clinical course and the response to immunomodulatory treatment Raising likelihood of neoplasia If muscle acetylcholine receptor (AChR) modulating antibody value is (or exceeds) 90% AChR loss and striational antibody is detected, thymoma is likely. Reflexive testing will include collapsin response-mediated protein-5-lgG Western blot, ganglionic AChR antibody, glutamic acid decarboxylase (GAD65) antibody, and voltage-gated potassium channel complex (VGKC) antibody (which are frequent with thymoma). Note: Single antibody tests may be requested in follow-up of patients with positive results documented in this laboratory.

**Interpretation:** The patient's autoantibody profile is more informative than the result of any single test for supporting a diagnosis of myasthenia gravis (MG), and for predicting the likelihood of thymoma (see MGETH / Myasthenia Gravis [MG] Evaluation, Thymoma). Muscle acetylcholine receptor (AChR) and striational autoantibodies are characteristic but not diagnostic of MG. One or both are found in 13% of patients with Lambert-Eaton Syndrome (LES), but P/Q-type calcium channel autoantibodies are very rare in MG. Results are sometimes positive in patients with neoplasia without evidence of neurological impairment. Titers are generally higher in patients with severe weakness, or with thymoma, but severity cannot be predicted by antibody titer. Test results for muscle acetylcholine receptor and striational antibodies may be negative for 6 to 12 months after MG symptom onset. Only 8% of nonimmunosuppressed patients with generalized MG remain seronegative beyond 12 months for all autoantibodies in the adult MG evaluation. Of those patients 38% will have the alternative muscle-specific receptor tyrosine kinase (MuSK)-specific autoantibody. MuSK antibody-positive patients lack thymoma, and have predominantly oculobulbar symptoms that respond to plasmapheresis and immunosuppressant therapy. They do not benefit from thymectomy.

**Reference Values:**

ACh RECEPTOR (MUSCLE) BINDING ANTIBODY

< or =0.02 nmol/L

ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES

0-20% (reported as __% loss of AChR)

STRIATIONAL (STRIATED MUSCLE) ANTIBODIES

Myasthenia Gravis (MG) Evaluation, Pediatric
Clinical Information: Myasthenia gravis (MG) is an acquired disorder of neuromuscular transmission caused by the binding of pathogenic autoantibodies to muscle's postsynaptic nicotinic acetylcholine receptor (AChR). In about 3% of cases the pathogenic antibody is directed at the functionally associated muscle-specific receptor tyrosine kinase (MuSK). The outcome is a critical loss of the AChR channel protein, which is required to activate the muscle action potential. Amongst North American Caucasian children (ie, aged 1-18), MG affects prepubertal boys and girls with equal frequency. Spontaneous remissions are relatively frequent. Females predominate (4.5:1) after puberty. Amongst black children with MG, females predominate (2:1) in all age groups, and remissions are infrequent, regardless of therapy. Congenital MG is a hereditary nonautoimmune disorder characterized by defects in AChR or other synaptic proteins. Autoimmune serology is indispensable for both initial evaluation and monitoring the course of patients with acquired disorders of neuromuscular transmission. The neurological diagnosis depends on the clinical context, electromyographic findings, and response to anticholinesterase administration. MG is confirmed more readily by a serological profile than by any single test. See Myasthenia Gravis: Pediatric Diagnostic Algorithm in Special Instructions.

Useful For: Recommended for initial investigation of patients presenting at less than age 20 with a defect of neuromuscular transmission Confirming that a recently acquired neurological disorder has an autoimmune basis Distinguishing acquired myasthenia gravis from congenital myasthenic syndromes (persistently seronegative) Providing a quantitative baseline for future comparisons in monitoring clinical course and response to immunomodulatory treatment Note: Single antibody tests may be requested in follow-up of patients with positive results documented in this laboratory.

Interpretation: Muscle acetylcholine receptor (AChR) autoantibodies are characteristic but not diagnostic of myasthenia gravis (MG). They are found in 13% of patients with Lambert-Eaton Syndrome (LES), which is rare in children. The patient's autoantibody profile is more informative than the result of any single test for supporting a diagnosis of MG. Titers of AChR antibodies are generally higher in patients with severe weakness, but severity cannot be predicted by antibody titer. Seronegativity is more frequent in children with prepubertal onset of acquired MG (33%-50%) than in adults (<10%). Thymoma is rare under age 20, and striational antibodies (see STR / Striational [Striated Muscle] Antibodies, Serum) also are rare, except in the context of MG related to neoplasia (usually thymoma or neuroblastoma), graft-versus-host disease, autoimmune liver disease, or D-penicillamine therapy. This laboratory has recently noted muscle-specific receptor tyrosine kinase antibody in children with "seronegative" acquired MG, but the frequency of this antibody in pediatric MG has not been determined.

Reference Values:
ACh RECEPTOR (MUSCLE) BINDING ANTIBODY
< or =0.02 nmol/L

ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES
0-20% (reported as __% loss of AChR)

Myasthenia Gravis (MG) Evaluation, Thymoma

Clinical Information: Myasthenia gravis (MG) is an acquired disorder of neuromuscular transmission caused by the binding of pathogenic autoantibodies to muscle's postsynaptic nicotinic acetylcholine receptor (AChR). Synaptic transmission fails when these pathogenic autoantibodies cause a critical loss of the AChR cation channel protein, which is required to activate the muscle action potential. It is estimated that approximately 20% of adult patients have a paraneoplastic basis for MG. Thymoma is the most common neoplasm, often occult at the onset of MG, its diagnosis may precede MG onset. Thymoma is thought to be an endogenous source of muscle and neuronal antigens that drive production of characteristic autoantibodies. Other autoimmune neurological disorders sometimes accompany thymoma, with and without MG, including neuromuscular hyperexcitability, autonomic neuropathy, especially gastrointestinal dysmotilities encephalopathy, subacute hearing loss, or polymyositis. MG can affect children as well as adults, but a paraneoplastic context is rare in children (neuroblastoma or thymoma are sometimes found). Some of the antibodies in this profile are not pathogenic (eg, antibodies directed at cytoplasmic epitopes accessible in solubilized ion channels, or sarcomeric proteins that constitute the striational antigens). Autoimmune serology is indispensable for initial evaluation and monitoring the course of patients with acquired MG. The neurological diagnosis depends on the clinical context, electromyographic findings, and response to anticholinesterase administration. MG is confirmed more readily by the individual patient's serological profile than by any single test. See Myasthenia Gravis: Thymoma Diagnostic Algorithm in Special Instructions.

Useful For: Investigating patients with suspected or proven thymoma, whether or not symptoms or signs of myasthenia gravis (MG) are present Serially monitoring patients for recurrence or metastasis after removal of thymoma Providing a quantitative autoantibody baseline for future comparisons in monitoring a patient's clinical course and the response to thymectomy and immunomodulatory treatment Assessing the likelihood of occult thymoma in a patient with an acquired disorder of neuromuscular or autonomic transmission Evaluating bone marrow transplant recipients with suspected graft-versus-host disease, particularly if there is evidence of weakness Confirming that a recently acquired neurological disorder has an autoimmune basis (eg, MG or dysautonomia)

Interpretation: A patient's autoantibody profile is more informative than the result of any single test for predicting the likelihood of thymoma, and for supporting a diagnosis of myasthenia gravis (MG) or other paraneoplastic neurological complication. Muscle acetylcholine receptor (AChR) and striational autoantibodies are characteristic but not diagnostic of MG in the context of thymoma. One or more antibodies in the MG/thymoma evaluation are positive in more than 60% of nonimmunosuppressed patients who have thymoma without evidence of any neurological disorder. Titers of muscle AChR and striational antibodies are generally higher in MG patients who have thymoma, but severity of weakness cannot be predicted by antibody titer. A rising antibody titer (or appearance of a new antibody specificity) following thymoma ablation suggests thymoma recurrence or metastasis, or development of an unrelated neoplasm. Antibodies specific for the alternative muscle autoantigen of MG, muscle-specific receptor tyrosine kinase, are not associated with thymoma.

Reference Values:

ACh RECEPTOR (MUSCLE) BINDING ANTIBODY
< or =0.02 nmol/L

ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES
0-20% (reported as __% loss of AChR)

STRIATIONAL (STRIATED MUSCLE) ANTIBODIES
CRMP-5-IgG WESTERN BLOT
Negative

ACHR GANGLIONIC NEURONAL ANTIBODY
< or = 0.02 nmol/L

NEURONAL (V-G) K+ CHANNEL AUTOANTIBODY
< or = 0.02 nmol/L

GAD65 ANTIBODY ASSAY
< or = 0.02 nmol/L

Clinical References:

Myasthenia Gravis (MG)/Lambert-Eaton Syndrome (LES) Evaluation

Clinical Information: Myasthenia gravis (MG) and Lambert-Eaton syndrome (LES) are acquired disorders of neuromuscular transmission. MG is caused by pathogenic autoantibodies binding to muscle's nicotinic acetylcholine receptor (ACHR) or, in a small minority of patients, muscle-specific receptor tyrosine kinase (MuSK); LES is caused by autoantibodies binding to motor nerve terminal's voltage-gated P/Q-type calcium channel. Synaptic transmission fails when autoantibodies cause a critical loss of junctional cation channel proteins that activate the muscle action potential. Both MG and LES can affect children (see MGEP / Myasthenia Gravis [MG] Evaluation, Pediatric) as well as adults, although LES is very rare in children. In adults MG is 10 times more frequent than LES, but it is sometimes difficult to distinguish the 2 disorders, clinically and electromyographically. In adults with MG, there is at least a 20% occurrence of thymoma or other neoplasm. Neoplasms associated with LES or MG are an endogenous source of the antigens driving production of the autoantibodies that characterize each disorder. LES is frequently associated with small-cell lung carcinoma (SCLC). Thus far, MuSK antibody has not been associated with any neoplasm. Autoimmune serology is indispensable for both the initial evaluation and monitoring of patients with acquired disorders of neuromuscular transmission. The neurological diagnosis depends on the clinical context and electromyographic findings, and is confirmed more readily by a serological profile than by any single test. Not all of the antibodies in this profile impair neuromuscular transmission (eg, N-type calcium channel antibodies, antibodies directed at cytoplasmic epitopes accessible in detergent solubilized P/Q-type calcium channels and muscle AChRs, or antibodies against sarcomeric proteins that constitute the striational antigens). See Myasthenia Gravis/Lambert Eaton Syndrome Diagnostic Algorithm in Special Instructions.

Useful For: Confirming the autoimmune basis of a defect in neuromuscular transmission (eg, myasthenia gravis [MG], Lambert-Eaton syndrome [LES]) Distinguishing LES from 2 recognized autoimmune forms of MG Raising the index of suspicion for cancer, particularly primary lung carcinoma (N-type calcium channel antibody) Providing a quantitative autoantibody baseline for future comparisons in monitoring a patient's clinical course and response to immunomodulatory treatment Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.
Interpretation: A patient's autoantibody profile is more informative than the result of any single test for supporting a diagnosis of Myasthenia Gravis (MG) or Lambert-Eaton syndrome (LES), and for predicting the likelihood of lung carcinoma. Muscle acetylcholine receptor (AChR) and striational antibodies are characteristic but not diagnostic of MG. One or both are found in 13% of patients with LES, but calcium channel antibodies are not found in MG (with exception of rare non-thymomatous paraneoplastic cases). Muscle AChR binding antibody is found in 90% of nonimmunosuppressed MG patients who have thymoma, and 80% have a striational antibody. Calcium channel antibodies have not been encountered with thymoma. The likelihood of thymoma is greatest when striational antibody is accompanied by a high muscle AChR modulating antibody value (> or =90% AChR loss). Detection of CRMP-5-IgG also is consistent with thymoma in patients not at risk for lung carcinoma. N-type calcium channel antibodies are more highly associated with primary lung cancer than P/Q-type. One or all of the autoantibodies in the MG/LES evaluation can occur with neoplasia without evidence of neurological impairment. Calcium channel antibodies may disappear soon after commencing immunosuppressant therapy. Other serological markers of lung cancer also may disappear. One or both calcium channel antibodies (P/Q and N) can occur with paraneoplastic and idiopathic cerebellar ataxia, encephalomyeloneuropathies, and autonomic neuropathy. Titters are generally higher in patients with severe weakness, but severity cannot be predicted by antibody titer. AChR and striational antibodies may be undetectable for 6 to 12 months after MG symptom onset and similarly P/Q-type calcium channel antibody may be undetectable for 6 to 12 months after LES onset. Only about 5% of nonimmunosuppressed adult patients with generalized MG remain seronegative for muscle AChR and striational autoantibodies beyond 12 months. The alternative muscle autoantigen, MuSK, accounts for approximately 1/3 of seronegative MG cases with predominantly oculobulbar symptoms.

Reference Values:

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh RECEPTOR (MUSCLE) BINDING ANTIBODY</td>
<td>&lt; or =0.02 nmol/L</td>
</tr>
<tr>
<td>ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES</td>
<td>0-20% (reported as ___% loss of AChR)</td>
</tr>
<tr>
<td>N-TYPE CALCIUM CHANNEL ANTIBODY</td>
<td>&lt; or =0.03 nmol/L</td>
</tr>
<tr>
<td>P/Q-TYPE CALCIUM CHANNEL ANTIBODY</td>
<td>&lt; or =0.02 nmol/L</td>
</tr>
<tr>
<td>STRIATIONAL (STRIATED MUSCLE) ANTIBODIES</td>
<td>&lt;1:120</td>
</tr>
</tbody>
</table>

Clinical References:

Myasthenia Gravis Evaluation with MuSK Reflex, Serum

Clinical Information: Fatigable weakness due to impaired synaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). The diagnosis is made by clinical and electromyographic criteria. Positive autoimmune serology must be interpreted in the clinical and electrophysiological context and response to anticholinesterase medication. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic acetylcholine receptor or its interacting proteins, such as muscle-specific kinase: MuSK).(1) Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (71% muscle acetylcholine receptor: AChR binding). Mayo Clinicâ€™s first-line serological evaluation detects muscle AChR antibody in 92% of nonimmunosuppressed patients with generalized weakness due to MG. In
adults with MG there is at least a 20% occurrence of thymoma or other neoplasm. If acetylcholine receptor (AChR) modulating antibodies are > or =90% and striational antibodies are > or =1:120, then there is an increased risk of thymoma, and AChR ganglionic neuronal autoantibody, glutamic acid decarboxylase autoantibody, neuronal voltage-gated potassium channel autoantibody, and collapsin response-mediated response-5-IgG may also be detected in that paraneoplastic context.(2) MuSK antibody is detectable in more than one-third of those seronegative for muscle AChR antibody (<4% of all patients).(3-4) Physiologically, MuSK is involved in integrating and stabilizing AChR clusters in the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Antibodies to LRP4 itself have been described in rare patients.(1) Females are generally affected by autoimmune MuSK MG more often than males. Onset can occur at any age (pediatric to elderly). Patients may derive limited benefit from anticholinesterase medication. The thymus is normal, and patients are generally not benefited by thymectomy. Antibody-lowering therapies are effective. Bulbar, facial, and respiratory weakness are prominent, and crises are common.(1,3,4) Six percent of nonimmunosuppressed patients with generalized MG lack demonstrable AChR or MuSK antibodies (double seronegative). However, as in autoimmune AChR MG and MuSK MG, testing for common organ-specific and nonorgan-specific autoantibodies is a valuable ancillary investigation in evaluating seronegative acquired generalized MG. General serological testing, coupled with family or personal history, will disclose autoimmune phenomena in 77% of those cases.(5) These disorders may include thyroid disease, type 1 diabetes, vitiligo, premature greying, rheumatoid arthritis, or lupus. Objective improvement in strength following a therapeutic trial of plasmapheresis or intravenous immune globulin would justify consideration of long-term immunosuppression.

**Useful For:** Diagnosis for autoimmune myasthenia gravis in adults and children Distinguishing autoimmune from congenital myasthenia gravis in adults and children Establishing a quantitative baseline value that allows comparison with future levels if weakness is worsening

**Interpretation:** A positive result, in the appropriate clinical context, confirms the diagnosis of autoimmune myasthenia gravis, with or without thymoma. Seropositivity justifies consideration of immunotherapy.

**Reference Values:**

- **ACh RECEPTOR (MUSCLE) BINDING ANTIBODY**
  - < or =0.02 nmol/L

- **ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES**
  - 0-20% (reported as __% loss of AChR)

- **STRIATIONAL (STRIATED MUSCLE) ANTIBODIES**
  - <1:120

**Clinical References:**


**MGRMI 37213**

**Myasthenia Gravis Interpretive Comments**

**Reference Values:**

Only orderable as part of a profile. For more information see MGRM / Myasthenia Gravis Evaluation with MuSK Reflex, Serum.
**MYB (6q23) Rearrangement FISH, Tissue**

**Clinical Information:** Salivary adenoid cystic carcinomas (ACC), although uncommon, are frequent among salivary gland malignancies. ACC is typically an aggressive tumor with a poor prognosis. Histologically, ACC show significant morphologic overlap with other salivary gland tumors, but have a much different clinical course. Because ACC requires a management distinct from histologically similar lesions, it is important to make an accurate diagnosis. Translocations between MYB (6q23.3) and NFIB (9p24) have been identified in a large proportion of primary salivary gland ACC. These alterations have not been identified in other salivary gland tumors. Therefore, separation of MYB, in the proper clinical and histologic context, is diagnostic for ACC and can be confirmed by FISH with MYB break-apart probes.

**Useful For:** Assessing for MYB gene rearrangements in patients with primary salivary gland carcinoma to aid in confirming or excluding the diagnosis of primary salivary gland adenoid cystic carcinomas

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the MYB locus. The presence of a MYB rearrangement in conjunction with the proper clinical and histologic features is diagnostic of adenoid cystic carcinomas (ACC). A confirmed diagnosis of ACC results in specific clinical management that may be distinct from the management of other salivary gland neoplasms. A negative result suggests no rearrangement of the MYB gene region at 6q23.3. The absence of a MYB rearrangement does not exclude the diagnosis of ACC, as a subset of ACCs do not show an MYB rearrangement.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Mycobacteria and Nocardia Culture**

**Clinical Information:** Mycobacteria species are responsible for significant morbidity and mortality in both immunocompromised and immunocompetent hosts. Mycobacterium tuberculosis is the causative agent of tuberculosis and it kills nearly 2 million people in the world each year. Nontuberculous mycobacteria such as Mycobacterium avium complex and Mycobacterium abscessus cause a variety of infections (eg, respiratory, skin, and soft tissue) and are important to detect and correctly identify in order to aid in clinical decision making. There are more than 170 recognized species of mycobacteria and identification of these organisms to the species level is often required to help guide appropriate therapy. Although there are direct detection methods available for Mycobacterium tuberculosis, growth of the organism on culture media is still necessary to allow for antimicrobial susceptibility testing. At this time, direct molecular detection methods are lacking for the nontuberculous mycobacteria and growth in culture is critical for identification and antimicrobial susceptibility testing. Nocardia species and other aerobic actinomycetes (eg, Tsukamurella species, Gordonia species, Rhodococcus species) are also important causes of disease and isolation of culture media is important to facilitate identification and antimicrobial susceptibility testing. Nocardia and the other aerobic actinomycetes grow well on mycobacterial medium and, therefore, ordering a mycobacterial culture is recommended when infection with this group of organisms is suspected.

**Useful For:** Detection and identification of Mycobacteria species, Nocardia species and other aerobic actinomycetes. Identification is performed using the Hologic/GenProbe AccuProbes for selected Mycobacteria species, MALDI-TOF mass spectrometry, or 500 base pair 16S rRNA gene sequencing. Mycobacterium tuberculosis complex species identification can be done upon request using rapid PCR targeting the regions of difference (RD) genomic areas.

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SGTF 35860

CTB 8205
**Interpretation:** A final negative report is issued after 60 days incubation. Positive cultures are reported as soon as detected.

**Reference Values:**
Negative


**ISMY 45265**

**Mycobacteria Ident by Sequencing (Bill Only)**

**Reference Values:**
This test is for billing purposes only. This is not an orderable test.

**CTBBL 82443**

**Mycobacterial Culture, Blood**

**Clinical Information:** Mycobacteremia occurs most often in immunocompromised hosts. The majority of disseminated mycobacterial infections are due to Mycobacterium avium complex but bacteremia can also be caused by other mycobacterial species including, but not limited to, Mycobacterium tuberculosis complex, Mycobacterium kansasii, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium scrofulaceum, Mycobacterium szulgai, and Mycobacterium xenopi.(1) Mycobacterial blood cultures may be indicated for patients presenting with signs and symptoms of sepsis, especially fever of unknown origin.

**Useful For:** Diagnosing mycobacteremia

**Interpretation:** A positive result may support the diagnosis of mycobacteremia.

**Reference Values:**
Negative
If positive, mycobacteria is identified.
A final negative report will be issued after 60 days of incubation.


**MTBRP 88807**

**Mycobacterium tuberculosis Complex, Molecular Detection, PCR**

**Clinical Information:** Each year, Mycobacterium tuberculosis accounts for approximately 1.4 million deaths and is responsible for 9 million newly diagnosed cases of tuberculosis worldwide. Mycobacterium tuberculosis is spread from person-to-person via respiratory transmission, and has the potential to become resistant to many or all of the antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of Mycobacterium tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect Mycobacterium tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid PCR assay detects Mycobacterium tuberculosis complex DNA directly from respiratory specimens and other specimens without waiting for growth in culture and, therefore, the results are available the same day the specimen is received in the laboratory.
Mycobacterial culture should always be performed in addition to the PCR assay. The PCR assay is rapid but the culture has increased sensitivity over the PCR assay. The PCR assay targets a unique sequence within the katG gene, which is present in members of the Mycobacterium tuberculosis complex. In addition, the assay can detect genotypic resistance to isoniazid mediated by mutations in the katG target, when present.

**Useful For:** Rapid detection of Mycobacterium tuberculosis complex DNA, preferred method Detection of Mycobacterium tuberculosis, when used in conjunction with mycobacterial culture

**Interpretation:** A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. Members of the Mycobacterium tuberculosis complex detected by this assay include Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium bovis Bacillus Calmette-Guerin, Mycobacterium africanum, Mycobacterium canetti, and Mycobacterium microti. Other species within the Mycobacterium tuberculosis complex (eg, Mycobacterium bovis subspecies caprae and Mycobacterium pinnepedi) should, in theory, be detected using the primer and probe sequences in this assay, but they have not been tested. This assay method does not distinguish between the species of the Mycobacterium tuberculosis complex. A negative result indicates the absence of detectable Mycobacterium tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG mutation will be reported when observed but lack of a katG mutation does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug.

**Reference Values:** Not applicable

**Clinical References:**
Mycobacterium tuberculosis complex. A negative result indicates the absence of detectable Mycobacterium tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG mutation will be reported when observed but lack of a katG mutation does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug.

**Reference Values:**
Not applicable


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**MTBPZ 56099**

**Mycobacterium tuberculosis Complex, Pyrazinamide Resistance by pncA DNA Sequencing**

**Clinical Information:** The protein product of the Mycobacterium tuberculosis complex pncA gene is an enzyme that is responsible for activation of the prodrug pyrazinamide (PZA). DNA sequencing of the Mycobacterium tuberculosis complex pncA gene can be used to detect mutations that correlate with in vitro PZA resistance. (1,2) The sequencing result can be available in as little as 1 day after the Mycobacterium tuberculosis complex isolate grows in culture, thereby providing a more rapid susceptibility result than the average 10 to 14 days required by phenotypic broth methods.

**Useful For:** Detection of genotypic resistance to pyrazinamide by Mycobacterium tuberculosis complex isolates

**Interpretation:** Polymorphisms in the pncA gene that have been previously correlated in our laboratory with pyrazinamide (PZA) resistance will be reported as "Mutation was detected in pncA suggesting resistance to pyrazinamide." Wild-type pncA or a silent pncA gene polymorphism (ie, no change in the amino acid translation) will be reported as "No mutation was detected in pncA." New polymorphisms in the pncA gene that have not previously been seen in our laboratory will require additional testing using a reference broth method to determine their correlation with PZA resistance.

**Reference Values:**
Pyrazinamide resistance not detected


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**MPA 81563**

**Mycophenolic Acid, Serum**

**Clinical Information:** Mycophenolate mofetil (CellCept) is a new immunosuppressive agent useful in organ transplantation. It is approved for use in renal, hepatic, and cardiac transplants. When mycophenolate mofetil enters the blood, it is immediately metabolized to the active drug, mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase and interferes with the de novo pathway of guanosine nucleotide synthesis selectively in lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. MPA acts in the same fashion as azathioprine, and MPA is suggested as replacement therapy for azathioprine. The drug is deactivated by the hepatic enzyme, uridine diphosphate glucuronosyltransferase to form mycophenolic acid glucuronide (MPA-G). The principle clinical problem encountered in MPA therapy is excessive
immunosuppression, which predisposes the patient to systemic infection. Measurement of the blood level of MPA and MPA-G can be useful to guide therapy. Monitoring is recommended immediately after transplant up to 3 weeks after therapy is initiated to evaluate dosing adequacy. Additional monitoring is indicated if the MPA level is not in the therapeutic range or if a major change in health status occurs.

**Useful For:** Monitoring therapy with CellCept to ensure adequate blood levels and avoid overimmunosuppression

**Interpretation:** Trough serum levels of mycophenolic acid (MPA) at steady-state (>2 weeks at the same dose) in the range of 1.0 to 3.5 mcg/mL indicate adequate therapy. Mycophenolic acid glucuronide (MPA-G) levels in the range of 35 to 100 mcg/mL indicate that the patient has normal uridine diphosphate glucuronosyltransferase (UGT) metabolic capacity. MPA-G levels are typically in the range of 100 to 250 mcg/mL during the 2 weeks following transplantation. MPA-G typically decreases after this initial post-transplant phase. Trough steady-state serum MPA levels >4.0 mcg/mL indicate that the patient is overimmunosuppressed and susceptible to systemic infections. Decreased dosages may be indicated in these cases. Low MPA levels and high MPA-G levels suggest that the patient has an active UGT metabolic capability; higher doses may be required to maintain therapeutic levels of MPA. Some patients have a high UGT metabolic capacity. These patients may require 1 gram or more 3 times a day to maintain trough serum MPA levels in the range of 1.0 mcg/mL to 3.5 mcg/mL. They are likely to have MPA-G levels >100 mcg/mL. MPA-G is inactive; MPA-G levels only describe the patient’s metabolic status. Patients who have low UGT conjugating capability may become overimmunosuppressed, indicated by a trough steady-state serum MPA level >4.0 mcg/mL and a MPA-G level <40 mcg/mL. Dose reduction or interval prolongation is indicated in this case.

**Reference Values:**

**MYCOPHENOLIC ACID (MPA)**

1.0-3.5 mcg/mL

**MPA GLUCURONIDE**

35-100 mcg/mL


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**Mycobacteria genitalium, Molecular Detection, PCR**

**Clinical Information:** Mycoplasma genitalium causes acute and chronic nongonococcal urethritis, cervicitis, and pelvic inflammatory disease. Culture isolation is technically challenging; PCR is the diagnostic test of choice.

**Useful For:** Rapid, sensitive, and specific identification of Mycoplasma genitalium from genitourinary and reproductive sources

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Mycoplasma genitalium tuf gene indicates the presence of Mycoplasma genitalium DNA in the specimen. A negative PCR result indicates the absence of detectable Mycoplasma genitalium DNA in the specimen, but does not rule-out infection as false-negative results may occur due to the following: inhibition of PCR, sequence variability underlying the primers or probes, or the presence of Mycoplasma genitalium in quantities below the limit of detection of the assay.

**Reference Values:** Not applicable

Mycoplasma hominis, Molecular Detection, PCR

Clinical Information: Mycoplasma hominis has been associated with a number of clinically significant infections, although it is also part of the normal genital flora. Mycoplasma hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may occur without specific treatment, in premature infants, clinical manifestations of meningoencephalitis have been reported. Mycoplasma hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. Mycoplasma hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. Mycoplasma hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extrapulmonary infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, Mycoplasma hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of Mycoplasma hominis infection in lung transplant recipients. PCR detection of Mycoplasma hominis is sensitive, specific, and provides same-day results. Although this organism can occasionally be detected in routine plate cultures, this is neither a rapid nor a sensitive approach to detection. Specialized cultures are more time consuming than the described PCR assay. The described PCR assay has replaced conventional culture for Mycoplasma hominis at Mayo Medical Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Mycoplasma hominis from synovial fluid, genitourinary, reproductive, lower respiratory sources, pleural/pleural fluid, pericardial fluid, and wound specimens

Interpretation: A positive PCR result for the presence of a specific sequence found within the Mycoplasma hominis tuf gene indicates the presence of Mycoplasma hominis DNA in the specimen. A negative PCR result indicates the absence of detectable Mycoplasma hominis DNA in the specimen, but does not rule-out infection as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Mycoplasma hominis in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum

Clinical Information: Mycoplasma pneumoniae is an important respiratory tract pathogen. Several syndromes have been associated with the infection including pharyngitis, tracheobronchitis, pneumonia, and inflammation of the tympanic membrane presenting as bulous myringitis. Mycoplasma pneumoniae accounts for approximately 20% of all cases of pneumonia. Classically, it causes a disease that has been described as primary atypical pneumonia. The disease is of insidious onset with fever, headache, and malaise for 2 to 4 days before the onset of respiratory symptoms. Most cases do not require hospitalization. Symptomatic infections attributable to this organism most commonly occur in children and young adults (ages 2-19 years).(1)

Useful For: An aid in the diagnosis of disease associated with Mycoplasma pneumoniae

Interpretation: Positive IgM results are consistent with acute infection, although false positives do occur (see Cautions). A single positive IgG result only indicates previous immunologic exposure. Negative results do not rule-out the presence of Mycoplasma pneumoniae-associated disease. The
specimen may have been drawn before the appearance of detectable antibodies. If testing is performed too early following primary infection, IgG and/or IgM may not be detectable. If a Mycoplasma infection is clinically indicated, a second specimen should be submitted in 14 to 21 days.

**Reference Values:**

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =0.90</td>
<td>(negative)</td>
<td>&lt; or =0.90</td>
</tr>
<tr>
<td>0.91-1.09</td>
<td>(equivocal)</td>
<td>0.91-1.09</td>
</tr>
<tr>
<td>&gt; or =1.10</td>
<td>(positive)</td>
<td>&gt; or =1.10</td>
</tr>
</tbody>
</table>

**IgM by IFA**

Negative (reported as positive or negative)

**Clinical References:** Smith T: Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc 1986;61:830-831

**Mycoplasma pneumoniae Antibody, CF (CSF)**

**Reference Values:**

**REFERENCE RANGE:** <1:1

**INTERPRETIVE CRITERIA:**

- <1:1 Antibody Not Detected
- > or = 1:1 Antibody Detected

Diagnosis of infections of the central nervous system is accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios for the infectious agent.

**Mycoplasma pneumoniae Culture**

**Clinical Information:** Mycoplasma pneumoniae is one of the principal etiologic agents responsible for primary atypical pneumonia (often called walking pneumonia) as well as more mild forms of upper respiratory illness. Primary atypical pneumonia may be a severely debilitating disease and may infect otherwise healthy individuals.

**Reference Values:**

Reference Range: Not isolated

**Mycoplasma pneumoniae IgA**

**Reference Values:**

Reference Ranges Mycoplasma IgA:

- 0 - 9 BU/mL
  - None Detected
  - There is no indication of M. pneumoniae infection.
- 10 - 20 BU/mL
Equivocal
Test a second sample, drawn two to four weeks later in parallel with the first sample. When second sample is equivocal the result should be considered as negative.

21 BU/mL and greater
Relevant detectable levels of IgA antibodies. Suggestive of current or chronic M. pneumoniae infection.

**Mycoplasma pneumoniae, Molecular Detection, PCR**

**Clinical Information:** Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community acquired pneumonia.(1) Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to Mycoplasma pneumoniae. The disease is usually self-limited although severe disease has been reported in immunocompromised patients.(2) Identification of Mycoplasma pneumoniae by culture-based methods is time consuming and insensitive. Serology based assays for Mycoplasma pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week and the IgM response in adults may be variable or it may be decreased in immunosuppressed individuals.(3,4) Confirmation of the disease may be dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing.(4)

Real-time PCR offers a rapid and sensitive option for detection of Mycoplasma pneumoniae DNA from clinical specimens.

**Useful For:** Diagnosis of infections due to Mycoplasma pneumoniae

**Interpretation:** A positive result indicates the presence of Mycoplasma pneumoniae. A negative result does not rule out the presence of Mycoplasma pneumoniae and may be due to the presence of inhibitors within the specimen matrix, or the presence of organisms at numbers below the limits of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**MYD88, L265P, Somatic Gene Mutation, DNA Allele-Specific PCR**

**Clinical Information:** Single point mutation in MYD88 L265P is present in 67% to 100% of patients with lymphoplasmacytic lymphoma and these patients typically have clinical manifestations of Waldenstromâ€™s macroglobulinemia (often designated LPL/WM).

**Useful For:** Establishing the diagnosis of lymphoplasmacytic lymphoma/Waldenstromâ€™s macroglobulinemia and helping to distinguish this low grade B-cell lymphoma from other subtypes

**Interpretation:** Mutation present or not detected; an interpretive report will be issued.

**Reference Values:**
Mutation present or absent based on expected mutant PCR product size. Concurrent amplification of wild type MYD88 fragment determined for sample amplification integrity. MYD88 gene (NCBI accession NM_002468.4).

**70138**

MYD88, L265P, Somatic Gene Mutation, DNA Allele-Specific PCR (Bill Only)

**Clinical Information:**

**Useful For:**

**Interpretation:**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**Clinical References:**

**FMGA**

57249

Myelin Assoc. Glycoprotein (MAG) Antibody w/Reflex to MAG-SGPG & MAG, EIA

**Reference Values:**

MAG Ab (IgM), Western Blot

Reference Range: Negative

MAG-SGPG Ab (IgM), EIA

Reference Range:

< or = 1:1600

MAG Ab (IgM), EIA

<1:1600

Reference ranges for MAG IgM Antibody:

Normal: <1:1600

Moderately Elevated: 1:1600-1:3200

Highly Elevated: >1:6400

**MDSF**

35285

Myelodysplastic Syndrome (MDS), FISH

**Clinical Information:** Myelodysplastic syndromes (MDS) primarily occur in the older adult population and have a yearly incidence of 30 in 100,000 in persons >70 years of age. These disorders are typically associated with a hypercellular bone marrow and low peripheral blood counts, and with
significant morbidity and mortality. The eventual clinical outcome for patients with MDS relates to either bone marrow failure or transformation to acute myeloid leukemia. MDS can be either primary (de novo) or secondary (due to previous treatment with alkylating or etoposide chemotherapy, with or without radiation). Cytogenetic studies can provide confirmatory evidence of clonality in MDS and can be used to provide clinical prognostic or diagnostic information. Clonal cytogenetic abnormalities are more frequently observed in cases of secondary MDS (80% of patients) than in primary MDS (40%-60% of patients). The common chromosomal abnormalities associated with MDS include: inv(3), -5/5q-, -7/7q-, +8, 13q-, and 20q-. These abnormalities can be observed singly or in concert. In addition, MLL rearrangements, t(1;3) and t(3;21) are more frequently associated with secondary MDS. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in MDS.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myelodysplastic syndromes or other myeloid malignancies Evaluating specimens in which standard cytogenetic analysis is unsuccessful Identifying and tracking known chromosome abnormalities in patients with myeloid malignancies and tracking response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values: An interpretive report will be provided.

Clinical References:

Myelodysplastic Syndrome by Flow Cytometry, Bone Marrow

Clinical Information: Myelodysplastic syndromes (MDS) encompass a heterogeneous group of clonal hematopoietic neoplasms characterized by cytopenias due to ineffective hematopoeisis, variable degrees of dysmyelopoietic morphologic features, and increased risks of evolution to acute myeloid leukemia. Per 2008 World Health Organization recommendations, a definitive diagnosis of MDS requires identification of 1 or more of the following findings: clear-cut morphologic features of dysplasia in > or ≥10% of the cells in 1 or more of the 3 hematopoietic lineages; increased (but <20%) blood or marrow blasts with or without Auer rods; and well-characterized clonal cytogenetic abnormalities.(3-4) However, at present, in approximately 50% of MDS patients, no informative or diagnostic clonal cytogenetic abnormalities are identified. Not infrequently, morphologic review of the patientâ€™s blood and marrow specimen is inconclusive. And yet it is important to distinguish MDS and other clonal myeloid neoplasms from other nonmalignant and nonneoplastic possibilities in the differential diagnosis such as medication effects or other toxic exposures, copper deficiency, infections, and left-shifted hematopoietic regeneration, among others. In such settings, when used in conjunction with appropriate clinical and morphologic findings, flow cytometry immunophenotyping analysis can provide additional diagnostic information to help distinguish an underlying clonal hematopoietic neoplasm from a reactive or secondary response.(2,5)

Useful For: Detecting increased blasts Characterizing blast phenotypes Identifying abnormal patterns of myeloid maturation as seen in myelodysplastic syndromes and other clonal myeloid neoplasms Providing additional adjunct diagnostic information in cases with equivocal or suspicious morphologic features for myelodysplastic syndrome (MDS), MDS/myeloproliferative neoplasms including chronic myelomonocytic leukemia, and other clonal myeloid neoplasms

Interpretation: The final interpretation integrates 1) the quantity of blasts; 2) blast phenotype with respect to CD13/HLA-DR expression and/or abnormal coexpression of CD2, CD7, and/or CD56; and 3) myeloid maturation patterns based on CD13/CD16 plot. In combination, the total number of abnormalities detected and the distinctiveness of the abnormalities themselves help determine the likelihood of
specimen involvement by a clonal myeloid neoplasm.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.


Myeloid Sarcoma, FISH, Tissue

Clinical Information: Myeloid sarcomas are tumors made up of myeloblasts or immature myeloid cells that occur in extramedullary sites or in bone. They can occur concurrently with acute or chronic myeloid leukemia (AML or CML) or may precede the leukemia or other myeloid neoplasms. They may also be the initial manifestation of relapse of a previously treated primary AML in remission. Due to this extramedullary presentation, the bone marrow may have a low number of myeloblasts due to a lack of bone marrow involvement. The most common abnormalities seen in myeloid sarcomas are fusion of RUNX1T1/RUNX1 [t(8;21)(q22;q22)], PML/RARA [t(15;17)(q24;q21)], BCR/ABL1 [t(9;22)(q34;q11.2)], inversion of MYH11/CBFB [inv(16)(q13.1q22)], and rearrangements of MLL [t(11q23;var)]. In general, AML patients with an inv(16), t(8;21), t(9;22) or t(15;17) have a favorable prognosis, while AML patients with a rearrangement of t(11q23) have an unfavorable prognosis. Thus, the detection of these abnormalities in an extramedullary presentation of AML can be prognostically important.

Useful For: Supporting the diagnosis of myeloid sarcoma when coordinated with a surgical pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a myeloid sarcoma. A negative result does not exclude the diagnosis of a myeloid sarcoma.

Reference Values:
An interpretive report will be provided.


Myeloma, FISH, Fixed Cells

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of myeloma: asymptomatic myeloma, smoldering myeloma, indolent myeloma, and multiple myeloma. Asymptomatic
Myeloma patients have nonspecific symptoms that may be attributed to other diseases. Generalized bone pain, anemia, numbness or limb weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate myeloma. In smoldering myeloma there is a monoclonal protein spike, but it is stable. Indolent myeloma is a slowly progressing myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

**Useful For:**
- Aiding in the diagnosis of new cases of multiple myeloma
- Identifying prognostic markers based on the abnormalities found

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MPO 80389**

**Myeloperoxidase Antibodies, IgG, Serum**

**Clinical Information:** Myeloperoxidase (MPO) enzyme is found in neutrophil primary granules and monocyte lysosomes. MPO catalyzes the conversion of hydrogen peroxide to hypochlorite and hypochlorous acid. MPO is encoded by a single gene that undergoes posttranslational modification to produce the active enzyme found in leukocytes. Autoantibodies to MPO (MPO antineutrophil cytoplasmic antibodies: ANCA) occur in several diseases and may be involved in the pathogenesis of vascular inflammation in patients with microscopic polyangiitis (MPA).(1,2) Patients with MPA often develop MPO ANCA and may present with azotemia secondary to glomerulonephritis (pauci-immune necrotizing glomerulonephritis). MPO ANCA are not specific for MPA, and also may be detected in patients with systemic lupus erythematosus with or without lupus nephritis, Goodpasture syndrome and Churg-Strauss syndrome. Lupus nephritis and Goodpasture syndrome, as well as Wegener granulomatosis may present with azotemia and progressive renal failure. It is not possible to distinguish among these diseases on the basis of clinical signs and symptoms; autoantibody testing may be helpful.

**Useful For:** Evaluating patients suspected of having immune-mediated vasculitis, especially microscopic polyangiitis (MPA), when used in conjunction with other autoantibody tests (see Cautions)

May be useful to follow treatment response or to monitor disease activity in patients with MPA

**Interpretation:** A positive result has a high predictive value for microscopic polyangiitis (MPA) in patients with negative test results for systemic lupus erythematosus (antinuclear antibodies) and Goodpasture syndrome (glomerular basement membrane antibody). A negative result significantly diminishes the likelihood that a patient has MPA.(3) While myeloperoxidase levels often decline following successful treatment of MPA, specific guidelines for this clinical purpose are not available.

**Reference Values:**
- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- ≥1.0 U (positive)
Reference values apply to all ages.

**Clinical References:**

**Myeloproliferative Neoplasm (MPN), JAK2 V617F with Reflex to CALR and MPL**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder

**Interpretation:** The results will be reported as 1 of the 4 following states: -Positive for JAK2 V617F mutation -Positive for CALR mutation -Positive for MPL mutation -Negative for JAK2 V617F, CALR, and MPL mutations Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
MUTYH

Clinical Information: Biallelic germline mutations in the MYH gene (official symbol MUTYH) cause MYH-associated polyposis (MAP) syndrome, an autosomal recessive form of inherited colorectal cancer. Approximately 15% to 20% of all colorectal cancer cases are thought to be due to heritable genetic causes. The 2 most common forms of hereditary colorectal cancer are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). FAP accounts for <1% of all colorectal cancer cases and HNPCC accounts for approximately 2% to 3% of all colorectal cancer. The proportion of inherited colorectal cancer cases attributable to MAP is not known at this time. Phenotypic overlap exists between MAP and FAP. However, patients with MAP tend to develop fewer adenomatous polyps (generally <100) than patients with classical FAP, who generally develop hundreds to thousands of polyps. Patients with biallelic MYH mutations are at risk for colorectal cancer and other extracolonic manifestations (upper gastrointestinal tumors, congenital hyperpigmentation of the retinal epithelium) similar to those observed in patients with FAP. Although patients with MAP typically present with multiple polyps, literature suggests that biallelic mutations have been seen in patients with early onset colorectal cancer. Therefore, screening for MYH should be considered in patients with early onset colorectal cancer in whom no DNA mismatch repair (MMR) defect has been identified. Literature suggests that monoallelic carriers may be at slightly increased risk for colon cancer, upper gastrointestinal cancer, and other tumors. Approximately 1% to 2% mixed European Caucasian individuals are predicted to carry an MYH mutation. Therefore, the reproductive partners of monoallelic and biallelic carriers should be offered carrier screening to adequately assess the risk of their offspring having MAP. The MYH gene is located on chromosome 1 and encodes a base excision repair protein that functions to repair oxidative DNA damage. This assay provides direct analysis of the Y165C and G382D mutations in the MYH gene. These 2 mutations account for approximately 85% of the disease-causing MYH mutations in affected mixed European Caucasian individuals. Refer to Hereditary Colorectal Cancer: Adenomatous Polyposis Syndromes, Mayo Medical Laboratories Communique 2004 Sep;29(9) for more information regarding diagnostic strategy. Also see Colonic Polyposis Syndromes Testing Algorithm in Special Instructions.

Useful For: Determining whether the clinical phenotype of multiple colorectal adenomas is due to biallelic MYH mutations in the affected individual Predictive testing and familial risk assessment by carrier screening for multiple colorectal adenomatous polyps when an MYH mutation has been identified in an affected family member

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.


MCA

Myocardial Antibodies, Serum

Clinical Information: Myocardial antibodies occur in the sera of patients who have acute rheumatic fever and carditis, or who have sustained mechanical (surgical or traumatic) or ischemic damage to myocardial tissue in the postcardiotomy and post myocardial infarction syndromes. In the "myocardial injury" syndromes, circulating myocardial antibodies become detectable 2 to 3 weeks after the injury in 30% (infarction) to 70% (postsurgical) of cases and remain detectable for 3 to 8 weeks. Myocardial
antibodies have been detected in some patients with idiopathic cardiomyopathy. The pathogenic significance of myocardial antibodies is not known.

**Useful For:** Evaluating patients suspected of having post cardiotomy or post myocardial infarction syndromes Evaluating patients suspected of having inflammatory cardiomyopathy

**Interpretation:** Elevated in 30% of myocardial injury patients by the 2nd or 3rd week

**Reference Values:**
Negative
If positive, results are titered.
Reference values apply to all ages.


**FMPP 91332**

**Myocarditis/Pericarditis Panel**

**Reference Values:**

**MYOCARDITIS-PERICARDITIS PANEL**

**COXSACKIE B(1-6) ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- > or = 1:8 Antibody Detected

Single titers of > or = 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

This test was developed and its performance characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.

**ECHOVIRUS ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- > or = 1:8 Antibody Detected

Single titers > or = 1:32 are indicative of recent infection. Titers of 1:8 and 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

This test was developed and its performance characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.

**INFLUENZA TYPES A AND B ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8
**INTERPRETIVE CRITERIA:**

<1:8 Antibody Not Detected

> or = 1:8 Antibody Detected

Single titers of > or = 1:64 are indicative of recent infection. Titers of 1:8 to 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis.

This test was developed and its performance characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.

**CHLAMYDOPHILA PNEUMONIAE ANTIBODIES (IgG, IgA, IgM)**

**REFERENCE RANGE:**

IgG <1:64

IgA <1:16

IgM <1:10

The immunofluorescent detection of specific antibodies to Chlamydophila pneumoniae may be complicated by cross-reactive antibodies, non-specific antibody stimulation, or past exposure to similar organisms such as C. psittaci and Chlamydia trachomatis. IgM titers of 1:10 or greater usually indicate recent infection, and any IgG titer may indicate past exposure. IgA is typically present at low titers during primary infection, but may be elevated in recurrent exposures or in chronic infection.

These assays were developed and their performance characteristics have been determined by Focus Diagnostics. They have not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

**MYGLS**

**Myoglobin, Serum**

**Clinical Information:** Myoglobin is a heme protein found in smooth and skeletal muscles. Serum myoglobin reflects a balance between intravascular release of myoglobin from muscle and renal clearance. Previously serum myoglobin had been advocated as a sensitive marker for early acute myocardial injury (eg, acute myocardial infarction: AMI). However, more recent studies indicate that other newer markers (eg, troponin) provide superior diagnostic utility in detecting early myocardial injury. Elevation of serum myoglobin may occur as a result of muscle trauma, resuscitation, myopathies, AMI, shock, strenuous body activity, or decreased elimination during renal insufficiency. Extreme elevations occur in rhabdomyolysis.

**Useful For:** Assessing muscle damage from any cause

**Interpretation:** Elevated myoglobin levels are seen in conditions of acute muscle injury.

**Reference Values:**

< or =90 mcg/L


**MYGLU**

**Myoglobin, Urine**

**Clinical Information:** Myoglobin is the oxygen-binding protein of striated muscle. Injury to skeletal or cardiac muscle results in the release of myoglobin. High concentrations appear very rapidly in the urine
in various conditions including some metabolic diseases. Conditions associated with myoglobinuria include: - Hereditary myoglobinuria - Phosphorylase deficiency - Sporadic myoglobinuria - Exertional myoglobinuria in untrained individuals - Crush syndrome - Myocardial infarction - Myoglobinuria of progressive muscle disease - Heat injury Urine myoglobin increases with muscle necrosis, but the clinical consequences are variable. Therefore, myoglobin can confirm a clinical diagnosis of myopathy, but an elevated urine excretion of myoglobin is not specific for a clinical disorder. In acute renal failure, an elevated urinary myoglobin can suggest a potential cause and, consequently, may indicate appropriate treatment courses.

**Useful For:** Confirming the presence of a myopathy associated with any 1 of the disorders listed in Clinical Information May suggest a myopathic cause for acute renal failure

**Interpretation:** Increased excretion of urinary myoglobin suggests the disorders listed in Clinical Information. Most clinically significant elevations are elevated 2 to 10 times normal. Visual pigmenturia occurs at myoglobin concentrations about 160 times normal (approximately 4,000 mcg/L). Renal toxicity depends on multiple factors such as renal perfusion and degree of acidity of urine.

**Reference Values:**
< or =21 mcg/L


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**FMYO 91544**

**MyoMarker Panel 1**

**Reference Values:**
Normal Range: Negative

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**FMYOP 91545**

**MyoMarker Panel 2**

**Clinical Information:** 1. Anti-Jo 1 Abs are found in subset of myositis patients characterized by interstitial lung disease, systemic polyarthritis, Raynaudâ€™s Phenomena, fever and Mechanicâ€™s Hand (anti-synthetase syndrome). 2. Anti-Jo 1 appears to be a marker for interstitial lung disease in polymyositis.

**Reference Values:**
Mi-2, PL-12, PL-7, EJ, OJ, SRP, Ku, U2 snRNP

Reference Range: Negative

Anti-PM/Scl Ab, Anti-Jo-1 Ab

Reference Range: <20

EIA Interpretation:

- Negative: <20 units
- Weak Positive: 20 â€“ 39 units
- Moderate Positive: 40 â€“ 80 units
- Strong Positive: >80 units

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**FMP3 58016**

**MyoMarker Panel 3**

**Reference Values:**
PL-7, PL-12, EJ, OJ, SRP, MI-2, Fibrillarin (U3 RNP), U2 snRNP, Ku:
Reference Range: Negative

Anti-Jo-1 Ab, TIF1 GAMMA (P155/140), MDA-5 (P140) (CADM-140), NXP-2 (P140), Anti-PM/Scl Ab, Anti-U1-RNP Ab, Anti-SS-A 52 kD Ab IgG:

Reference Range: <20

EIA Interpretation:
- Negative: <20 units
- Weak Positive: 20–39 units
- Moderate Positive: 40–80 units
- Strong Positive: >80 units

DDITF

Myxoid/Round Cell Liposarcoma, 12q13 (DDIT3 or CHOP) Rearrangement, FISH, Tissue

Clinical Information: Myxoid/round cell liposarcoma is the second most common subtype of liposarcoma, accounting for more than one third of all liposarcomas and representing about 10% of all adult soft-tissue sarcomas. Myxoid/round cell liposarcoma is described as a malignant tumor composed of uniform round to oval shaped primitive nonlipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma with a characteristic branching vascular pattern. A unique chromosome translocation, t(12;16)(q13;p11), resulting in a fusion of the DDIT3 gene (also known as CHOP or GADD153) on chromosome 12 and the FUS gene (also referred to as TLS) on chromosome 16, is the key genetic aberration in myxoid/round cell liposarcoma. More than 90% of myxoid/round cell liposarcoma are cytogenetically characterized by this translocation. In rare cases, a variant t(12;22)(q13;q12) has been described in which DDIT3 (CHOP) fuses with EWS, a gene highly related to FUS.

Useful For: Aiding in the diagnosis of myxoid/round cell liposarcoma by detecting a neoplastic clone associated with gene rearrangement involving the DDIT3 (CHOP) gene region at 12q13

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the DDIT3 (CHOP) probe. A positive result is consistent with a subset of myxoid/round cell liposarcoma. A negative result suggests no rearrangement of the DDIT3 (CHOP) gene region at 12q13. However, this result does not exclude the diagnosis of myxoid/round cell liposarcoma.

Reference Values:
An interpretive report will be provided.

Clinical References:

G6SW

N-Acetylgalactosamine-6-Sulfatase, Leukocytes

Clinical Information: Mucopolysaccharidosis IVA, (MPS IVA, Morquio A syndrome) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent N-acetylgalactosamine-6-sulfate
sulfatase (GALNS) enzyme activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Accumulation of GAGs (previously called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms of MPS IVA are widely variable and affect multiple body systems. Clinical features may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Treatment options are mostly limited to symptom management, however, more recently available enzyme replacement therapy has shown to be effective in improving some function and quality of life for individuals with Morquio A. Estimates of the incidence of Morquio A syndrome range from 1 in 200,000 to 1 in 300,000 live births. A diagnostic workup in an individual with MPS IVA typically demonstrates elevated levels of urinary GAGs and increased keratan sulfate and chondroitin-6-sulfate detected via quantitative and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Morquio B is a genetically distinct disorder caused by a deficiency of beta-galactosidase and has a significant number of overlapping clinical features with Morquio A. Enzyme analysis is necessary to distinguish between the 2 types. Reduced or absent activity of N-acetylgalactosamine-6-sulfate sulfatase enzyme in leukocytes and/or fibroblasts can confirm a diagnosis of MPS IVA. Sequencing of the GALNS gene allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members.

**Useful For:** Assisting in the diagnosis of Morquio A disease

**Interpretation:** Very low enzyme activity levels are consistent with Morquio A disease.

**Reference Values:**

> or =92 nmol/17 hour/mg protein

**Clinical References:**


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**N-Acetylgalactosamine-6-Sulfate Sulfatase, Fibroblasts**

**Clinical Information:** Mucopolysaccharidosis IVA, (MPS IVA, Morquio A syndrome) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans, GAGs). Accumulation of GAGs (previously called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms of MPS IVA are widely variable and affect multiple body systems. Clinical features may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Treatment options are mostly limited to symptom management, however, more recently available enzyme replacement therapy has shown to be effective in improving some function and quality of life for individuals with Morquio A. Estimates of the incidence of Morquio A syndrome range from 1 in 200,000 to 1 in 300,000 live births. A diagnostic workup in an individual with MPS IVA typically demonstrates elevated levels of urinary GAGs and increased keratan sulfate and chondroitin-6-sulfate detected via quantitative and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Morquio B is a genetically distinct disorder caused by a deficiency of beta-galactosidase and has a significant number of overlapping clinical features with Morquio A. Enzyme analysis is necessary to distinguish between the 2 types. Reduced or absent activity of N-acetylgalactosamine-6-sulfate sulfatase enzyme in leukocytes or fibroblasts can confirm a diagnosis of MPS IVA. Sequencing of the GALNS gene allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members.
Useful For: Assisting in the diagnosis of Morquio A disease

Interpretation: Very low enzyme levels are consistent with Morquio A disease.

Reference Values:
> or =163 nmol/17 hour/mg protein


NAPRO
37057

N-acetylprocainamide, Serum

Reference Values:
Only orderable as part of a profile. For more information see PROC / Procainamide and NAPA, Serum.

NAT2
83389

N-Acetyltransferase 2 Gene (NAT2), Full Gene Sequence

Clinical Information: Arylamine N-acetyltransferase type 2 (NAT2) is a highly polymorphic phase 2 metabolic enzyme that conjugates hydrazine derivatives and aromatic amine drugs with acetyl-groups. NAT2 also is involved in the acetylation and activation of some procarcinogens.(1) Individuals acetylate drugs at different rates by NAT2, and are described as having slow, intermediate, or fast acetylator phenotypes. A gradient exists in which the prevalence of slow acetylator phenotypes increases with decreasing distance to the equator. Near the equator, up to 80% of individuals may be slow acetylators, while in some more northern countries, as few as 10% of the population may have the slow acetylator phenotype. A number of drugs are metabolized by NAT2 including procainamide, dapsone, nitrazepam, hydralazine, zonisamide, and isoniazid. Isoniazid is used to treat and prevent tuberculosis, and is still used as a primary treatment agent. Adverse reactions with isoniazid, which include nausea, drug-induced hepatitis, peripheral neuropathy, and sideroblastic anemia, are associated more often with a slow NAT2 acetylator phenotype. These individuals may require a lower dose to avoid adverse reactions. The NAT2 gene contains a single intronless exon of 870 base pairs and encodes 290 amino acids. NAT2 is highly polymorphic and contains 16 known single nucleotide polymorphisms (SNPs) and 1 single base pair deletion. These polymorphisms are combined into 36 known haplotype alleles. Each individual haplotype is predictive of either a fast or slow acetylator phenotype. Individuals with 2 fast haplotypes are predicted to be extensive (normal) metabolizers, while those with 1 fast and 1 slow haplotype are intermediate metabolizers, and those with 2 slow haplotypes are poor metabolizers.(2,3) Studies with patients who have different acetylator haplotypes have correlated the ratio of plasma N-acetylisoniazid/isoniazid drug concentrations with haplotypes, with slow and intermediate acetylators having lower ratios than fast acetylators.(4) NAT2 Allele Nucleotide Change Amino Acid Change Predicted Acetylator Phenotype *4 None None Fast *5A 341T->C 481C->T I114T Slow *5B 341T->C 481C->T 803A->G I114T K268R Slow *5C 341T->C 803A->G I114T K268R Slow *5D 341T->C I114T Slow *5E 341T->C 590G->A I114T R197Q Slow *5F 341T->C 481C->T 759C->T 803A->G I114T K268R Slow *5G 282C->T 481C->T 803A->G I114T K268R Slow *5H 341T->C 481C->T 803A->G 859Del I114T K268R S287 Frameshift Slow *5I 341T->C 411A->T 859Del I114T K268R Slow *5J 282C->T 341T->C 590G->A I114T R197Q Slow *6A 282C->T 590G->A R197Q Slow *6B 590G->A R197Q Slow *6C 282C->T 590G->A G R197Q K268R Slow *6D 111T->C 282C->T 590G->A R197Q Slow *6E 481C->T 590G->A R197Q Slow *7A 857G->A G286E Slow *7B 590G->A R197Q Slow *7C 282C->T 857G->A G286E Slow *800 533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1406

Current as of July 8, 2016 11:28 am CDT
Useful For: Identifying patients who may require isoniazid dosing adjustments

Interpretation: The wild-type (normal) genotype for NAT2 is *4. This is the most commonly occurring allele in some, but not all, ethnic groups.(5) Individuals are classified as being slow, intermediate, or fast acetylators depending on their diplotypes. Slow acetylators have 2 slow haplotypes, fast acetylators have 2 fast haplotypes, and intermediate acetylators have 1 of each. Slow acetylators receiving isoniazid therapy should be monitored for signs of toxicity. Dose reductions may be considered for both slow and intermediate acetylators. However, it should be verified that the reduced isoniazid dose produces serum levels within the therapeutic range.

Reference Values:
An interpretive report will be provided.


NAT2O

N-Acetyltransferase 2 Gene (NAT2), Full Gene Sequence, Saliva

Clinical Information: Arylamine N-acetyltransferase type 2 (NAT2) is a highly polymorphic phase 2 metabolic enzyme that conjugates hydrazine derivatives and aromatic amine drugs with acetyl-groups. NAT2 also is involved in the acetylation and activation of some procarcinogens.(1) Individuals acetylate drugs at different rates by NAT2, and are described as having slow, intermediate, or fast acetylator phenotypes. A gradient exists in which the prevalence of slow acetylator phenotypes increases with decreasing distance to the equator. Near the equator, up to 80% of individuals may be slow acetylators, while in some more northern countries, as few as 10% of the population may have the slow acetylator phenotype. A number of drugs are metabolized by NAT2 including procainamide, dapsone, nitrazepam, hydralazine, zonisamide, and isoniazid. Isoniazid is used to treat and prevent tuberculosis, and is still used as a primary treatment agent. Adverse reactions with isoniazid, which include nausea, drug-induced hepatitis, peripheral neuropathy, and sideroblastic anemia, are associated more often with a slow NAT2 acetylator phenotype. These individuals may require a lower dose to avoid adverse reactions. The NAT2 gene contains a single intronless exon of 870 base pairs and encodes 290 amino acids. NAT2 is highly polymorphic and contains 16 known single nucleotide polymorphisms and 1 single base-pair deletion. These polymorphisms are combined into 36 known haplotype alleles. Each individual haplotype is predictive of either a fast or slow acetylator phenotype. Individuals with 2 fast haplotypes are predicted to be extensive (normal) metabolizers, while those with 1 fast and 1 slow haplotype are intermediate metabolizers, and those with 2 slow haplotypes are poor metabolizers.(2,3) Studies with patients who have different acetylator haplotypes have correlated the ratio of plasma N-acetylisoniazid/isoniazid drug concentrations with haplotypes, with slow and intermediate acetylators having lower ratios than fast acetylators.(4) NAT2 Allele Nucleotide Change Amino Acid Change Predicted Acetylator Phenotype

*4 None None Fast
*5A 341T->C 481C->T I114T Slow
*5B 341T->C 481C->T 803A->G I114T K268R Slow
*5C 341T->C 803A->G I114T K268R Slow
*5D 341T->C 1114T R197Q Slow
*5F 341T->C 411A->T 481C->T 803A->G I114T L137F K268R Slow
*5G 282C->T 341T->C 481C->T 803A->G I114T K268R Slow
*5H 341T->C 481C->T 759C->T 803A->G I114T K268R Slow
*5I 282C->T 341T->C 803A->G I114T K268R Slow
*5J 282C->T 341T->C 759C->T 803A->G I114T K268R Slow
*6A 341T->C 481C->T 803A->G K268R Slow
*6B 282C->T 341T->C 803A->G I114T R197Q Slow
*6C 282C->T 341T->C 803A->G R197Q K268R Slow
*6D 1114T->C 282C->T 590G->A R197Q K268R Slow
*6E 481C->T 590G->A R197Q K268R Slow
*6F 282C->T 481C->T 590G->A R197Q K268R Slow
*6G 282C->T 481C->T 590G->A R197Q K268R Slow
*6H 282C->T 590G->A R197Q K268R Slow
*6I 282C->T 590G->A R197Q K268R Slow
*6J 282C->T 590G->A R197Q K268R Slow
*6K 282C->T 590G->A R197Q K268R Slow
*6L 282C->T 590G->A R197Q K268R Slow
*6M 282C->T 590G->A R197Q K268R Slow
*6N 282C->T 590G->A R197Q K268R Slow
*6O 282C->T 590G->A R197Q K268R Slow
*6P 282C->T 590G->A R197Q K268R Slow
*6Q 282C->T 590G->A R197Q K268R Slow
*6R 282C->T 590G->A R197Q K268R Slow
*6S 282C->T 590G->A R197Q K268R Slow
*6T 282C->T 590G->A R197Q K268R Slow
*6U 282C->T 590G->A R197Q K268R Slow

This information is current as of July 8, 2016 11:28 am CDT.
282C->T None Fast *14A 191G->A R64Q Slow *14B 191G->A 282C->T R64Q Slow *14C 191G->A
341T->C 481C->T 803A->G R64Q I114T K268R Slow *14D 191G->A 282C->T 590G->A R64Q
R197Q Slow *14E 191G->A 803A->G R64Q K268R Slow *17 434A->C Q145P
Undetermined *18 845A->C K282T Undetermined *19 190C->T R64W Undetermined

**Useful For:** Identifying patients who may require isoniazid dosing adjustments Genotyping patients who prefer not to have venipuncture done

**Interpretation:** The wild-type (normal) genotype for NAT2 is *4. This is the most commonly occurring allele in some, but not all, ethnic groups.(5) Individuals are classified as being slow, intermediate, or fast acetylators depending on their diplotype. Slow acetylators have 2 slow haplotypes, fast acetylators have 2 fast haplotypes, and intermediate acetylators have 1 of each. Slow acetylators receiving isoniazid therapy should be monitored for signs of toxicity. Dose reductions may be considered for both slow and intermediate acetylators. However, it should be verified that the reduced isoniazid dose produces serum levels within the therapeutic range.

**Reference Values:**
An interpretive report will be provided.


**N-Methylhistamine, 24 Hour, Urine**

**Clinical Information:** N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most, but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3 Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and tryptase, alpha or beta (TRYPT / Tryptase, Serum).

**Useful For:** Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

**Interpretation:** Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit...
concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation. UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in spot-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

Reference Values:
0-5 years: 120-510 mcg/g creatinine
6-16 years: 70-330 mcg/g creatinine
>16 years: 30-200 mcg/g creatinine


FNTPX 57308  N-Telopeptide, Cross-Linked, Serum

Reference Values:
Adult Male: 5.4-24.2 nM BCE Premenopausal, Adult Female: 6.2-19.0 nM BCE

The target value for treated post-menopausal adult females is the same as the premenopausal reference interval.

BCE = Bone Collagen Equivalent

FINA 91447  NAbFeron (IFNB-1) Neutralizing Antibody Test

Useful For: Detection of antibodies to interferon-B-1

Reference Values:
Normal titer: <1:20
Mild/Moderate titer: > or = 1:20 - < or = 1:100
High titer: >1:100


NADS 80864  NADH Dehydrogenase Stain (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**FNAD** 80761  
**Nadolol, Serum/Plasma**  
**Reference Values:** Reporting limit determined each analysis  
Synonym(s): Corgard  
Mean steady-state plasma levels following a daily regimen:  
- 80 mg: 26 à€“ 36 ng/mL  
- 160 mg: 52 à€“ 74 ng/mL  
- 320 mg: 154 à€“ 191 ng/mL

**FNALO** 91784  
**Naloxone - Total (Conjugated/Unconjugated), Screen, Urine**  
**Reference Values:** Reporting limit determined each analysis (screen and confirmation)  
- Naloxone à€“ Total ng/mL  
  Synonym(s): Narcan  
- Naloxone à€“ Confirmation ng/mL  
  Synonym(s): Narcan

**NARC** 82026  
**Narcolepsy-Associated Antigen, HLA-DQB1 Typing, Blood**  
**Clinical Information:** Narcolepsy is a neurological condition affecting about 0.02% of African American, Caucasian, and Japanese individuals. It is characterized by excessive daytime somnolence and abnormal rapid eye movement (REM) sleep. Cataplexy (weakness precipitated by emotions, especially laughter) is present in 64% to 79% of patients with narcolepsy. Studies have identified DQB1*06:02 as a useful marker of narcolepsy. DQB1*06:02 is found in 90% to 95% of African American, Caucasian, and Japanese patients with narcolepsy who also have cataplexy (narcolepsy type 1), but only in 45% to 50% of patients with narcolepsy without cataplexy (narcolepsy type 2). It must also be clearly understood that about 25% of normal people have this gene. Because DQB1*06:02 is present in the normal population, no test for an HLA gene constitutes a test for narcolepsy. A more reliable approach would be to consider that, in an appropriate patient who has cataplexy, the absence of the strongly associated DQB1*06:02, provides good evidence that the patient does not have narcolepsy. However, its absence does not rule-out narcolepsy without cataplexy (narcolepsy type 2).  
**Useful For:** Ruling out a diagnosis of narcolepsy  
**Interpretation:** If DQB1*06:02 is not detected, the narcolepsy-associated antigen test result will be reported as negative for DQB1*06:02. If the allele is detected, the result will be reported as positive for DQB1*06:02.  
**Reference Values:** An interpretive report will be provided.  
Natural Killer (NK) Cytotoxicity Profile

Clinical Information: Natural killer (NK) cell cytotoxicity includes spontaneous cytotoxicity against target cells, typically lacking surface major histocompatibility complex class I expression, cytokine-stimulated cytotoxicity (also called lymphokine-associated cytotoxicity), and antibody-dependent cellular cytotoxicity. NK cell cytotoxic function is a key aspect of innate immunity and critical to maintenance of immune function, particularly with regard to viral infections (herpes viruses) and tumor surveillance. Cytotoxic NK cells typically express CD16 at high levels and CD56 at very low levels (CD16+56+) and account for the majority of circulating NK cells, while cytokine-producing NK cells express CD56 abundantly but little to no CD16 (CD56brightCD16+/−) expression. Cytotoxic NK cells contain cytotoxic granules expressing proteins such as perforin, granzyme A and B and granulysin, which participate in the effector cytotoxic function. T- and B-Cell Quantitation by Flow Cytometry: Normal immunity requires a balance between the activities of various lymphocyte subpopulations with different effector and regulatory functions. Different immune cells can be characterized by unique surface membrane antigens described by a cluster of differentiation nomenclature (eg, CD3 is an antigen found on the surface of T lymphocytes). Abnormalities in the number and percent of T (CD3), T-helper (CD4), T-suppressor (CD8), B (CD19), and natural killer (CD16+CD56) lymphocytes have been described in a number of different diseases. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. NK cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(5) and during summer compared to winter.(6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Natural Killer (NK) Cytotoxicity Profile: -Assessment of patients with recurrent, severe herpes viral infections, primary or secondary hemophagocytic lymphohistiocytosis, and suspected or known monogenic defects affecting the NK cell compartment (approximately 30 known defects cause either functional or classic NK cell deficiency) -Evaluation of immune reconstitution post hematopoietic cell transplantation and post immunomodulatory therapy T- and B-Cell Quantitation by Flow Cytometry: -Monitoring CD4 counts and assessing immune deficiencies

Interpretation: Cytotoxic activity (% killing) is reported for a series of titrating effector (E) to target (T) ratios. Reference values for each E:T ratio obtained as an average of a cohort of healthy individuals is provided with the report. Unmeasurable lytic activity or activity <1.5 U is compatible with cellular immunodeficiency. T- and B-Cell Quantitation by Flow Cytometry: When the CD4 count falls below 500 cells/mcL, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended.

Reference Values: The appropriate age-related reference values will be provided on the report.


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**Natural Killer (NK)/Natural Killer T (NKT) Cell Subset Panel**

**Clinical Information:** Natural killer (NK) cells are derived from pluripotent hematopoietic stem cell precursors, but develop independently of the thymus. They comprise a key lymphocyte subset (approximately 10%-15% of peripheral blood mononuclear cells) and are a constituent of the innate immune system, since these cells do not rearrange their germline DNA to obtain specificity. NK cells serve an important role in host defense against viral infections, as well as tumor surveillance. They are also a component of the adaptive immune response through cytokine production. NK cell functions are governed by a balance between activating receptors and inhibitory receptors. NK cells are identified by expression of different cell-surface receptors and they are not a homogeneous population.(1) In general, the most common combination of surface markers used to identify the majority of NK cells is the absence of CD3 (CD3-), along with expression of CD56 (neural cell adhesion molecule) and CD16 (low-affinity IgG Fc receptor-FcgammaRIII). However, not all NK cells express the CD56 and CD16 markers uniformly and, therefore, can be divided into subsets based on expression of these 2 molecules.(2) The CD16+ CD56+/-(dim or negative) that are CD3- are referred to as cytotoxic NK cells, while the CD56+ (bright) CD16- NK cells are called regulatory or cytokine secreting NK cells.(3) These are not only phenotypically and functionally distinct subsets but also developmentally separate. The majority of human NK cells (approximately 90%) have dim expression of CD56 and moderate to high levels of CD16, as well as perforin and granzymes (2 proteins mediating cytolytic activity), and are therefore high in cytotoxic capability. The remaining minority (approximately 10%) of NK cells are the CD56(bright) cytokine-producing NK cells. Therefore, cytotoxicity and cytokine production are the major functions of NK cells. Cytotoxicity can be subdivided into (1) natural cytotoxicity directed largely toward virally infected cells or tumor cells, in the absence of prior stimulation or immunization, and (2) antibody-dependent cellular cytotoxicity (ADCC) directed against antibody-coated target cells.(4) Circulating NK cells are enriched for the CD56(dim) phenotype, while within the lymph nodes, NK cells are largely CD56(bright). This differential localization is related to the pattern of homing receptors expressed on NK cells: CD56(dim) NK cells express homing markers for inflamed peripheral sites, while CD56(bright) NK cells express receptors for secondary lymphoid organs. The majority of circulating human NK cells, which have cytotoxic function and phenotype (CD56(dim)), are CD27-, while the CD56(bright) cells are CD27+. Therefore, the absence of CD27 expression identifies cytotoxic effector cells within the mature NK cell subsets.(5) Other markers are: --NKp46 (CD335) is a marker expressed on the majority of human NK cells and is an activating receptor involved in nonmajor histocompatibility complex (MHC)-restricted natural NK cytotoxicity. It is expressed in all resting and activated NK cells, including the minor CD56(bright) cytokine-producing population. NKp46 is considered to be involved in tumor cell eradication in vivo. --NKG2D is an activating receptor expressed on all NK cells, as well as on NKT cells. NKG2D has been described as being relevant in tumor surveillance and organ
transplantation.(6) --CD69 is a marker for NK-cell activation and triggers NK-mediated cytolytic activity and sustains NK-cell activation.(7) --CD95 (Fas or APO-1) is a marker expressed on a variety of immune cells, including lymphocytes and NK cells. CD95 is involved in mediating programmed cell death or apoptosis and has been shown to associate with NK cell regulatory function in multiple sclerosis.(8) --CD107a and CD107b (lyosomal-associated membrane proteins 1 and 2: LAMP-1 and LAMP-2) expression are markers of NK cell functional activity and correlate with both cytokine production and NK-cell-mediated lysis of target cells.(9) --Perforin, granzyme A, and granzyme B are components of the cytolytic granules in NK cells and associated with NK cell cytotoxic function, while interferon gamma (IFN-gamma) is produced by NK cells on activation.(10) --NK cells also secrete other cytokines including tumor necrosis factor alpha (TNF-alpha), interleukin-1 (IL-1), IL-3, and granulocyte monocyte-colony stimulating factor (GM-CSF). Natural killer T (NKT) cells represent a specialized T-cell population that is distinct from conventional T cells. They express an invariant T-cell receptor (TCR) that recognizes self and bacterial glycosphingolipid antigens presented by the MHC class I-like molecule, CD1d.(11) The development of NKT cells is also unique from regular T cells, as NKT cell precursors are positively selected by CD4+CD8+ cortical thymocytes and the signaling pathways differ from the conventional T cells. Activated NKT cells rapidly produce large amounts of Th1 and Th2 cytokines that transactivate other immune components and, therefore, NKT cells are involved in both innate and adaptive immune responses.(11) NK cell deficiencies can be present as part of a larger immunological syndrome or as an isolated deficiency. Some of the primary (monogenic) immunodeficiencies that affect NK cell function or numbers include autoimmune lymphoproliferative syndrome (ALPS) related to CASP8 (caspase 8 mutations); familial hemophagocytic lymphohistiocytosis (FHL) types 2, 3, and 4 due to mutations in the PPF1 (encoding perforin), UNC13D (encoding the Munc13-4 protein), and STX11 (encoding syntaxin -11), respectively; Hermansky-Pudlak syndrome (AP3B1); Papillon-Lefèvre syndrome (CTSC, cathepsin C); nuclear factor kappa-beta essential modulator deficiency (NEMO) due to mutations in the IKKBKG gene; severe combined immunodeficiencies due to mutations in the IL-2RG, JAK3, ADA, PNP, ADK2 genes; bare lymphocyte syndrome (TAP2 gene); X-linked inhibitor of apoptosis deficiency (XIAP gene); X-linked lymphoproliferative disease (XLP): XLP-1 (due to mutations in the SAP gene); Griscelli syndrome (RAB27A gene); Chediak-Higashi syndrome (LYST gene); and Wiskott-Aldrich syndrome (WAS gene).(12) Patients with X-linked inhibitor of apoptosis protein (XIAP) deficiency have been variably reported as having either normal numbers of NKT cells (13) or low numbers of NKT cells.(14) The apparent discrepancy in the numbers of NKT cells is likely related to the difference in size of the sample control groups and disease stage of patients between the 2 reports. At the present time, the role of XIAP in development of NKT cells has not been clearly delineated. The isolated NK cell deficiencies include the absolute NK cell deficiency (ANKD), the classic NK cell deficiency (CNKD), and the functional NK cell deficiency (FNKD). NK cell function is absent in ANKD and CNKD and deficient in FNKD, while NK cells are present in the latter, but absent in the former 2 conditions. NKT cells are absent only in ANKD and present in both CNKD and FNKD.(12) NK cell dysfunction has also been reported in systemic juvenile rheumatoid arthritis and macrophage activation syndrome.(15) There is also more data emerging on the pathogenic role of NK cells in atopic and autoimmune diseases.(4) HIV-1 patients show a gradual loss of NK cells that correlates with disease progression. There is a selective loss of CD56(dim) NK cells, while the numbers of CD56(bright) NK cells remain the same. There appears to be a defect in differentiation from immature CD56- NK cells to mature CD56(dim) NK cells (16), with an expansion of the former (CD56-CD16+) NK cells in HIV viremic patients.(17) Differential mobilization of NK-cell subsets has also been reported related to acute exercise, with CD56(bright) NK cells being less responsive than CD56(dim) NK cells and the ratio of CD56(bright):CD56(dim) favors the former at least up to 1-hour postexercise.(18) NK cells also play an important role in regulating viral infections, and their deficiency predisposes to susceptibility with herpes virus infections. NKG2D expression has been reported to decrease during human CMV infection.(19) NK cells that express inhibitory receptors to self-MHC class I molecules are called â€œlicensedâ€• NK cells lack receptors for self-MHC class I and are hyporesponsive. Contrary to the hypothesis that â€œlicensedâ€• NK cells are key for viral immunity, the depletion of â€œlicensedâ€• NK cells impairs control of viremia, suggesting that these cells are critical for protection against viral infection. NK-cell lymphocytosis is seen in NK-neoplasias, extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia, and blastic NK-cell lymphoma. Chronic NK-cell lymphocytosis (CNKL) is an indolent disorder characterized by proliferation of CD3-CD56+CD16- NK cells. Epstein-Barr virus (EBV) can infect nonneoplastic NK cells(20), and there is an expansion of CD16+CD56(dim) NK cells. Chronic active EBV infection involving NK cells can present with severe inflammatory and necrotic skin reactions typically associated with EBV+ NK-cell lymphoproliferative
Useful For: Quantitation of NK/NKT cell subsets as well as quantitation of specific cell-surface and intracellular proteins required for NK cell function. The assay provides both absolute and relative quantitation of various NK-cell subsets relative to total NK cells (NK cell subsets) or total lymphocytes (NKT cells) and can be used for assessment in the following clinical contexts: HIV, primary immune deficiencies with NK cell defects, NK-cell lymphocytosis, solid-organ transplantation, immune reconstitution following bone marrow or hematopoietic cell transplantation, evaluation of NK cells in neoplasias, only for quantitation (not for diagnosis or classification of NK cell malignancies).

Interpretation: Interpretive comments will be provided, where applicable, along with reference range values for adult samples. Since a separate pediatric reference range could not be established at this time, interpretation of pediatric samples will be made using the adult reference range as an approximate guideline. For the surface marker and intracellular protein expression on natural killer (NK) subsets, relevant values that are abnormal will be provided in a table format within the interpretation along with textual interpretive comments. If results for surface and/or intracellular subsets are quantitatively normal, then only interpretive comments will be provided without actual numeric data. Clients may request numerical data for specific subsets that are not included within the report through the Laboratory Director.

Reference Values: The appropriate age-related reference values will be provided on the report. Pediatric reference values are not available and therefore, interpretation will be based on adult ranges with appropriate cautionary statements in the interpretation.

Natural Killer (NK)/Natural Killer T (NKT) Cell Subsets, Quantitative

Clinical Information: Natural killer (NK) cells are derived from pluripotent hematopoietic stem cell precursors, but develop independently of the thymus. They comprise a key lymphocyte subset (approximately 10%-15% of peripheral blood mononuclear cells) and are a constituent of the innate immune system, since these cells do not rearrange their germline DNA to obtain specificity. NK cells serve an important role in host defense against viral infections, as well as tumor surveillance. They are also a component of the adaptive immune response through cytokine production. NK cell functions are governed by a balance between activating receptors and inhibitory receptors. NK cells are identified by expression of different cell-surface receptors and they are not a homogeneous population.(1) In general, the most common combination of surface markers used to identify the majority of NK cells is the absence of CD3 (CD3-), along with expression of CD56 (neural cell adhesion molecule) and CD16 (low-affinity IgG Fc receptor-FcgammaRIII). However, not all NK cells express the CD56 and CD16 markers uniformly and, therefore, can be divided into subsets based on expression of these 2 molecules.(2) The CD16+ CD56+/-(dim or negative) that are CD3- are referred to as cytotoxic NK cells, while the CD56+ (bright) CD16- NK cells are called regulatory or cytokine secreting NK cells.(3) These are not only phenotypically and functionally distinct subsets but also developmentally separate. The majority of human NK cells (approximately 90%) have dim expression of CD56 and moderate to high levels of CD16, as well as perforin and granzymes (2 proteins mediating cytolytic activity), and are therefore high in cytotoxic capability. The remaining minority (approximately 10%) of NK cells are the CD56(bright) cytokine-producing NK cells. Therefore, cytotoxicity and cytokine production are the major functions of NK cells. Cytotoxicity can be subdivided into (1) natural cytotoxicity directed largely toward virally infected cells or tumor cells, in the absence of prior stimulation or immunization, and (2) antibody-dependent cellular cytotoxicity (ADCC) directed against antibody-coated target cells.(4) Circulating NK cells are enriched for the CD56(dim) phenotype, while within the lymph nodes, NK cells are largely CD56(bright). This differential localization is related to the pattern of homing receptors expressed on NK cells: CD56(dim) NK cells express homing markers for inflamed peripheral sites, while CD56(bright) NK cells express receptors for secondary lymphoid organs. The majority of circulating human NK cells, which have cytotoxic function and phenotype (CD56(dim)), are CD27-, while the CD56(bright) cells are CD27+. Therefore, the absence of CD27 expression identifies cytotoxic effector cells within the mature NK cell subsets.(5) Natural killer T (NKT) cells represent a specialized T-cell population that is distinct from conventional T cells. They express an invariant T-cell receptor (TCR) that recognizes self and bacterial glycosphingolipid antigens presented by the MHC class I-like molecule, CD1d.(11) The development of NKT cells is also unique from regular T cells, as NKT cell precursors are positively selected by CD4+CD8+ cortical thymocytes and the signaling pathways differ from the conventional T cells. Activated NKT cells rapidly produce large amounts of Th1 and Th2 cytokines that transactivate other immune components and, therefore, NKT cells are involved in both innate and adaptive immune responses.(11) NK cell deficiencies can be present as part of a larger immunological syndrome or as an isolated deficiency. Some of the primary (monogenic) immunodeficiencies that affect NK cell function or numbers include autoimmune lymphoproliferative syndrome (ALPS) related to CASP8 (caspase 8 mutations); familial hemophagocytic lymphohistiocytosis (FHL) types 2, 3, and 4 due to mutations in the PFP1 (encoding perforin), UNC13D (encoding the Munc13-4 protein) and STX-11 (encoding syntaxin -11), respectively; Hermansky-Pudlak syndrome (AP3B1); Papillon-Lefevre syndrome (CTSC, cathepsin C); nuclear factor kappa-beta essential modulator deficiency (NEMO) due to mutations in the IKBKG gene; severe combined immunodeficiencies due to mutations in the IL-2RG, JAK3, ADA, PNP, ADK2 genes; bare lymphocyte syndrome (TAP2 gene); X-linked inhibitor of apoptosis deficiency (XIAP gene); X-linked lymphoproliferative disease (XLP): XLP-1 (due to mutations in the SAP gene); Griscelli syndrome (RAB27A gene); Chediak-Higashi syndrome (LYST gene); and Wiskott-Aldrich syndrome (WAS gene).(12) Patients with X-linked inhibitor of apoptosis protein (XIAP) deficiency have been variably reported as having either normal numbers of NKT cells (13) or low numbers of NKT cells.(14) The apparent discrepancy in the numbers of NKT cells is likely related to the difference in size of the sample control groups and disease stage of patients between the 2 reports. At the present time, the role of XIAP in development of NKT cells has not been clearly delineated. The isolated NK cell deficiencies include the absolute NK cell deficiency (ANKD), the classic NK cell deficiency...
(CNKD), and the functional NK cell deficiency (FNKD). NK cell function is absent in ANKD and CNKD and deficient in FNKD, while NK cells are present in the latter but absent in the former 2 conditions. NKT cells are absent only in ANKD and present in both CNKD and FNKD. (12) NK cell dysfunction has also been reported in systemic juvenile rheumatoid arthritis and macrophage activation syndrome. (15) There is also more data emerging on the pathogenic role of NK cells in atopic and autoimmune diseases. (4) HIV-1 patients show a gradual loss of NK cells that correlates with disease progression. There is a selective loss of CD56(dim) NK cells, while the numbers of CD56(bright) NK cells remain the same. There appears to be a defect in differentiation from immature CD56- NK cells to mature CD56(dim) NK cells (16), with an expansion of the former (CD56-CD16+) NK cells in HIV viremic patients. (17) Differential mobilization of NK-cell subsets has also been reported related to acute exercise, with CD56(bright) NK cells being less responsive than CD56(dim) NK cells and the ratio of CD56(bright):CD56(dim) favors the former at least up to 1-hour post-exercise. (18) NK cells also play an important role in regulating viral infections, and their deficiency predisposes to susceptibility with herpes virus infections. NKG2D expression has been reported to decrease during human CMV infection. (19) NK cells that express inhibitory receptors to self-MHC class I molecules are called â€œlicensedâ€• which means they are functionally more responsive to stimulation, while â€œunlicensedâ€• NK cells lack receptors for self-MHC class I and are hyporesponsive. Contrary to the hypothesis that â€œlicensedâ€• NK cells are key for viral immunity, the depletion of â€œunlicensedâ€• NK cells impairs control of viremia, suggesting that these cells are critical for protection against viral infection. NK-cell lymphocytosis is seen in NK-neoplasias, extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia, and blastic NK-cell lymphoma. Chronic NK-cell lymphocytosis (CNKL) is an indolent disorder characterized by proliferation of CD3-CD56+CD16- NK cells. Epstein-Barr virus (EBV) can infect nonneoplastic NK cells, and there is an expansion of CD16+CD56(dim) NK cells. Chronic active EBV infection involving NK cells can present with severe inflammatory and necrotic skin reactions typically associated with EBV+ NK-cell lymphoproliferative disease. (21)

**Useful For:** Quantitation of ONLY the major NK-cell subsets relative to total NK cells (NK cell subsets) or total lymphocytes (NKT cells) and can be used for assessment in the following clinical contexts: HIV, primary immune deficiencies with NK cell defects, NK-cell lymphocytosis, solid-organ transplantation, immune reconstitution following bone marrow or hematopoietic cell transplantation, evaluation of NK cells in neoplasias, only for quantitation (not for diagnosis or classification of NK cell malignancies). This assay does not measure cell-surface or intracellular proteins on NK/NKT cell subsets. Use NKSP if assessing NK/NKT cell subsets as well as specific surface and intracellular protein expression.

**Interpretation:** Interpretive comments will be provided, where applicable, along with reference range values for adult samples. Since a separate pediatric reference range could not be established at this time, interpretation of pediatric samples will be made using the adult reference range as an approximate guideline.

**Reference Values:**
The appropriate age-related reference values will be provided on the report. Pediatric reference values are not available and therefore, interpretation will be based on adult ranges with appropriate cautionary statements in the interpretation.

**Clinical References:**

**Nectarine (Prunus spp) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Nefazodone (Serzone)**

**Reference Values:**

Expected Nefazodone concentrations on recommended daily dosage regimens: 100 - 4000 ng/mL

**Neisseria gonorrhoea, Miscellaneous Sites, by Nucleic Acid Amplification (GEN-PROBE)**

**Clinical Information:** Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common sexually transmitted infection (STI), with 301,174 cases of gonorrhea reported to CDC in 2009.(1,2) Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence).(1,2) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance.(2) Culture was previously considered to be the gold standard test for diagnosis of Neisseria gonorrhoeae infection. However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid
amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Neisseria gonorrhoeae

**Interpretation:** A positive result indicates the presence of rRNA of Neisseria gonorrhoeae. A negative result indicates that rRNA for Neisseria gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (e.g., culture for Neisseria gonorrhoeae), if appropriate.

**Reference Values:**

Negative

**Clinical References:**

**Neisseria gonorrhoeae Antibody, CF (Serum)**

**Reference Values:**

REFERENCE RANGE: <1:8 Antibody not detected

INTERPRETIVE CRITERIA: <1:8 Antibody not detected
> or = 1:8 Antibody detected

Titers > or = 1:8 suggest either gonococcal infection or asymptomatic colonization. Antibodies recognizing Neisseria gonorrhoeae are apparently unprotective, since reinfection frequently occurs.

**Neisseria gonorrhoeae by Nucleic Acid Amplification (GEN-PROBE)**

**Clinical Information:** Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common sexually transmitted infection (STI), with 301,174 cases of gonorrhea reported to the CDC in 2009. Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal
bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (e.g., women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence).(1,2) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance.(2) Culture was previously considered to be the gold standard test for diagnosis of Neisseria gonorrhoeae infection. However, organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(2-5) Immunoassays and nonamplification DNA tests are also available for Neisseria gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT.(2-5) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.(2-5) Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detection of Neisseria gonorrhoeae

Interpretation: A positive result indicates the presence of rRNA of Neisseria gonorrhoeae. A negative result indicates that rRNA for Neisseria gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (e.g., culture for Neisseria gonorrhoeae), if appropriate.

Reference Values:

Negative

Clinical References:
This assay measures serum IgG antibodies recognizing polysaccharide antigens from the four Neisseria meningitidis serogroups included in the licensed meningococcal vaccine. The meningococcal vaccine response is best evaluated by testing pre-vaccination and post-vaccination samples in parallel. A two-fold or greater increase for at least two sero-groups is expected when comparing post-vaccination to pre-vaccination results. N. meningitidis IgG levels peak approximately one month post-vaccination, but decline markedly by two years.

**Neonatal Bilirubin, Serum**

**Clinical Information:** Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect one or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes Type I and Type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In Type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

**Interpretation:** The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is <20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

**Reference Values:**

**DIRECT**

> or =12 months: 0.0-0.3 mg/dL

Reference values have not been established for patients who are <12 months of age.

**TOTAL**

<1 month: not established

1 month-17 years: < or =1.0 mg/dL

> or =18 years: < or =1.2 mg/dL

**NervePath Consult, Level IV, Wet Tissue (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**NervePath Consult, Outside Slide (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**NervePath Consult, w/Comprehensive Review of History (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**NervePath Consult, w/Slide Preparation (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**NervePath Consult, w/USS Prof (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**Nettle, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
| 6     | > or =100| Strongly positive Reference values apply to all ages.


NEURF

**Neuraminidase, Fibroblasts**

**Clinical Information:** Sialidosis, also known as mucolipidosis I, is an autosomal recessive lysosomal storage disorder (LSD) resulting from a deficiency of the enzyme neuraminidase. Clinical presentation can vary and phenotypes are typically categorized by age of onset. Type I is considered to be the milder form of sialidosis and is characterized by a cherry-red spot on the retina, progressive decreased acuity, impaired color vision, or night blindness. Neurologic problems include gait abnormalities and poorly controlled myoclonus. Type II sialidosis is distinguished from type I by the presence of dysmorphic features, including coarse facies, hepatosplenomegaly, and dysostosis multiplex, early age of onset, and its more rapid disease progression. Developmental delay is frequently present in type II sialidosis. The congenital form is typically associated with hydrops. Galactosialidosis is an autosomal recessive lysosomal storage disease associated with a combined deficiency of neuraminidase and beta-galactosidase secondary to a defect in the cathepsin A protein. Clinical features are those typically associated with LSD including coarse facial features, cherry-red spots, and skeletal dysplasia. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal and ophthalmologic disorders, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features, hepatosplenomegaly, and heart valve problems. The juvenile/adult form is characterized by progressive neurologic degeneration, ataxia, cognitive disability, and/or angiokeratomas. Most of the juvenile/adult onset cases have been found in individuals of Japanese ancestry. A diagnosis of galactosialidosis is obtained by demonstrating a combined deficiency of neuraminidase and beta-galactosidase in lymphocytes or cultured skin fibroblasts.

**Useful For:** Aids in the diagnosis of sialidosis and galactosialidosis

**Interpretation:** Specimens with activity >0.10 nmol/min/mg protein are considered to be normal. Specimens with activity < or =0.10 nmol/min/mg protein are considered to be abnormal and suggestive of neuraminidase deficiency. Molecular confirmation is recommended.

**Reference Values:**

>0.10 nmol/min/mg Prot

**Clinical References:** 1. Thomas GH: Chapter 140: Disorders of Glycoprotein Degradation: Alpha-Mannosidosis, Beta-Mannosidosis, Fucosidosis, and Sialidosis. In The Metabolic Basis of
Neuroblastoma, 2p24 (MYCN) Amplification, FISH

Clinical Information: Neuroblastoma is a solid tumor that occurs in early childhood and is usually found in the adrenal glands, but rarely is found in other areas of the body. Approximately 25% of all neuroblastomas have amplification of the MYCN oncogene, located on chromosome 2 at p24.1. Amplification of the MYCN oncogene correlates with an unfavorable prognosis and aggressive disease. This test is not diagnostic for neuroblastoma. Other tumors including medulloblastoma, retinoblastoma, astrocytoma, and small cell lung cancer may have amplification of MYCN.

Useful For: As a prognostic factor for patients with neuroblastoma As an aid to treatment decisions in some patients with neuroblastoma

Interpretation: MYCN gene amplification is detected when the percent of cells with an abnormality exceeds the normal cutoff for the MYCN probe. A positive result is consistent with MYCN gene amplification. A negative result suggests no MYCN gene amplification. However, this result does not exclude the diagnosis of neuroblastoma.

Reference Values: An interpretive report will be provided.

metastatic disease involving the bone marrow is identified, FISH testing on the bone marrow can be performed to evaluate for MYCN status in the tumor.

**Useful For:** Aids in identifying metastatic disease in patients with a neuroblastoma that has been previously determined to be positive for the MYCN oncogene

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of metastatic disease. The absence of an abnormal clone does not rule out the presence of metastatic disease.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Neurofilament (SMI31), Immunostain Without Interpretation**

**Clinical Information:** Neurofilament antibody clone SMI 31 reacts with a phosphorylated epitope on neurofilament H and, to a lesser degree, neurofilament M. Both of these proteins contain multiple tandemly repeated serine phosphorylation sites. Clone SMI 31 reacts with thick and thin axons and specific dendrites such as basket cell dendrites. SMI 31 may also stain neuronal cell bodies in pathological conditions.

**Useful For:** Differentiating neurons (neurofilament positive) from glia (neurofilament negative)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order 70012 / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Please contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Neuroimmunology Antibody Follow-up, Serum**

**Clinical Information:** Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. The most commonly recognized cancers in this context are small-cell lung carcinoma (SCLC), thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin's lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin's lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Four classes of autoantibodies are recognized: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmic (Perkinje cell cytoplasmic antibody, type 1 [PCA-1], PCA-2, PCA-Tr, CRMP-5,
amphiphysin, and striational) - Glial nuclear (anti-glial nuclear antibody) - Plasma membrane cation channel Antibodies (neuronal P/Q-type and N-type calcium channel and muscle acetylcholine receptor autoantibodies). These autoantibodies are potential effectors of neurological dysfunction. Seropositive patients usually present with subacute neurological symptoms and signs. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome (LES), myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

**Useful For:** Monitoring patients who have previously tested positive for 1 or more antibodies in a Neuroimmunology Laboratory evaluation

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1) <1:240
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2) <1:240
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) <1:240
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) <1:240
- Purkinje Cell Cytoplasmic Antibody, Type Tr (PCA-Tr) <1:240
- Amphiphysin Antibody <1:240
- CRMP-5-IgG <1:240
- Striational (Striated Muscle) Antibodies <1:60
- Paraneoplastic Autoantibody Western Blot Confirmation Negative
- CRMP-5-IgG Western Blot Negative

**CATION CHANNEL ANTIBODIES**
- N-Type Calcium Channel Antibody < or =0.03 nmol/L
- P/Q-Type Calcium Channel Antibody < or =0.02 nmol/L
- ACh Receptor (Muscle) Binding Antibody < or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
ACh Receptor (Muscle) Modulating Antibodies
0-20% (reported as __% loss of AChR)

GAD65 ANTIBODY ASSAY
< or =0.02 nmol/L

Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin, ANNA-1, ANNA-2, ANNA-3, PCA-1, PCA-2, PCA-Tr, or CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Note: Titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, and cranial neuropathy and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 or 507-266-5700 to request CRMP-5 Western blot.

Neuroimmunology Antibody Follow-up, Spinal Fluid

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response, and serve as serological markers of paraneoplastic autoimmunity. The most commonly recognized cancers in this context are small-cell lung carcinoma (SCLC), thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin's lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin's lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Three classes of autoantibodies are recognized in the spinal fluid analysis: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmatic (Purkinje cell cytoplasmic antibody, type 1 [PCA-1]; PCA-2; PCA-Tr, CRMP-5, and amphiphysin) -Glial nuclear (anti-glial nuclear antibody: AGNA) Seropositive patients usually present with subacute neurological symptoms and signs. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome (LES), myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal gangliitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

Useful For: Monitoring patients who have previously tested positive for 1 or more antibodies in a Neuroimmunology Laboratory evaluation

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no known autoantibodies predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibodies to be detected, each predictive of the same cancer.

Reference Values:
ANTINEURONAL NUCLEAR ANTIBODY-Type 1 (ANNA-1)
<1:2
ANTINEURONAL NUCLEAR ANTIBODY-Type 2 (ANNA-2)  
<1:2

ANTINEURONAL NUCLEAR ANTIBODY-Type 3 (ANNA-3)  
<1:2

PURKINJE CELL CYTOPLASMIC ANTIBODY, Type 1 (PCA-1)  
<1:2

PURKINJE CELL CYTOPLASMIC ANTIBODY, Type 2 (PCA-2)  
<1:2

PURKINJE CELL CYTOPLASMIC ANTIBODY, Type Tr (PCA-Tr)  
<1:2

AMPHIPYSIN ANTIBODY  
<1:2

CRMP-5-IgG  
<1:2

PARANEOPLASTIC AUTOANTIBODY WESTERN BLOT CONFIRMATION  
Negative (reported as positive or negative)

Neuron-restricted patterns of IgG staining that do not fulfill criteria for the listed autoantibodies may be reported as "unclassified antineuronal IgG." If detected, newly identified autoantibody specificities may be reported. Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

**NEEVP**

**Neurologic Enzyme Evaluation**

**Clinical Information:** Several RBC enzymes are known to cause a nonspherocytic hemolytic anemia (HA). The most common cause of these is glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency. Four other RBC enzymes that cause HA have also been associated with hereditary myopathic or neurologic disorders. These enzymes are phosphofructokinase, triosephosphate isomerase, phosphoglycerate kinase, and glutathione synthase. Kinetic enzyme assays are available for the first 3 disorders. Quantitative measurement of glutathione substitutes for analysis of the enzyme glutathione synthase.

**Useful For:** Evaluating patients who have a hemolytic process that is associated with some neurologic findings

**Interpretation:** Definitive results and an interpretive report will be provided. Significant abnormal values typically are 25% of values obtained for a normal individual.

**Reference Values:**
Definitive results and an interpretive report will be provided.


**NMOCC**

**Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Cell-Binding**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1427
Assay, CSF

Clinical Information: Neuromyelitis optica (NMO, sometimes called Devic disease) is a severe, relapsing, autoimmune, inflammatory, and demyelinating central nervous system disease that predominantly affects optic nerves and the spinal cord. The disorder is now recognized as a spectrum of autoimmunity targeting the astrocytic water channel aquaporin-4 (AQP4). NMO spectrum disorders (NMOSD) may involve the brain and brainstem with symptoms of encephalopathy (particularly in children). The initial symptoms may be bouts of intractable nausea and vomiting. Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Prior to introducing a serological biomarker for NMO, the disorder was thought to be confined exclusively to the optic nerves and spinal cord, that the clinical course was monophasic, and that NMO was a subset of multiple sclerosis (MS). The discovery of a highly specific disease marker for NMO, neuromyelitis optica (NMO)/aquaporin-4(AQP4)-IgG (NMO-IgG/AQP4-IgG, helped to define the full clinical spectrum of NMOSD and distinguish these disorders from MS. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). Within 5 years, 50% of patients lose functional vision in at least 1 eye or are unable to walk independently. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-IFN, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Detection of NMO-IgG by cell-binding assay allows distinction of NMOSD (73% are positive) from MS (0% positive), and is indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack, thereby reducing attack frequency and disability in the future.

Useful For: Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Distinguishing NMOSD from multiple sclerosis early in the course of disease

Interpretation: A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 6 months if NMOSD is suspected. This autoantibody is not found in healthy subjects.

Reference Values:
Negative


NMOSCS

61715

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Cell-Binding Assay, Serum

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease, is a severe, relapsing, autoimmune inflammatory, and demyelinating central nervous system disease that predominantly affects optic nerves and the spinal cord. The disorder is now recognized as a spectrum of autoimmunity targeting the astrocytic water channel aquaporin-4 (AQP4). NMO spectrum disorders (NMOSD) may involve the brain and brainstem with symptoms of encephalopathy (particularly in children). The initial symptoms may be bouts of intractable nausea and vomiting. Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Prior to introducing a serological biomarker for NMO, the disorder was thought to be confined exclusively to the optic nerves and spinal cord, that the clinical course was monophasic, and that
NMO was a subset of multiple sclerosis (MS). The discovery of a highly specific disease marker for NMO, NMO-IgG/AQP4-IgG helped to define the full clinical spectrum of NMOSD and distinguish these disorders from MS. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). Within 5 years, 50% of patients lose functional vision in at least 1 eye or are unable to walk independently. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Detection of NMO IgG by cell-binding assay allows distinction of NMOSD (73% are positive) from MS (0% positive), and is indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack, thereby reducing attack frequency and disability in the future.

**Useful For:** Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Distinguishing NMOSD from multiple sclerosis early in the course of disease

**Interpretation:** A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 6 months if NMOSD is suspected. This autoantibody is not found in healthy subjects.

**Reference Values:**
Negative


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**Neuron-Specific Enolase (NSE), Serum**

**Clinical Information:** Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron specific enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ-specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF), are often elevated in diseases which result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum of CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jacob Disease. NSE might also have utility as a prognostic marker in neuronal injury. There is, for example, increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, in particular when caused by hypoxic insult. NSE is also frequently overexpressed by neural crest-derived tumors. Up to 70% of patients with small cell lung carcinoma (SCLC) have elevated serum NSE concentrations at diagnosis, and approximately 90% of patients with advanced SCLC will have serum levels above the healthy reference range. Other neuroendocrine tumors with frequent expression of NSE include carcinoids (up to 66% of cases), islet cell tumors (typically <40% of cases), and neuroblastoma (exact frequency of NSE expression unknown). NSE levels in NSE-secreting neoplasms correlate with tumor mass and tumor metabolic activity. High levels have therefore some negative prognostic value. Falling or rising levels are often correlated with tumor shrinkage or recurrence, respectively.

**Useful For:** A follow-up marker in patients with neuron-specific enolase-secreting tumors of any type An auxiliary test in the diagnosis of small cell lung carcinoma An auxiliary test in the diagnosis of
carcinoids, islet cell tumors and neuroblastomas. An auxiliary tool in the assessment of comatose patients

**Interpretation:** Serum neuron-specific enolase (NSE) measurement has its greatest utility in the follow-up of patients with tumors of any type that have been shown to secrete NSE. With successful treatment, serum concentrations should fall with a half-life of approximately 24 hours. Persistent NSE elevations in the absence of other possible causes (see Cautions) suggest persistent tumor. Rising levels indicate tumor spread, or in patients who had previously become NSE negative, recurrence. In the context of a patient with a lung mass, disseminated malignancy of unknown origin or symptoms suggestive of paraneoplastic disease without identifiable tumor, elevated NSE suggests an underlying small cell lung carcinoma (SCLC). In patients with suspected carcinoid, islet cell tumor, or neuroblastoma, who have no clear elevations in the primary tumor markers used to diagnose these conditions, an elevated serum NSE level supports the clinical suspicion. -Carcinoid: chromogranin A, urinary 5-hydroxyindoleacetic acid, serum/blood 5-hydroxytryptamine -Islet cell tumors: variety of peptide and amine-derived hormones, chromogranin A -Neuroblastoma: vanillylmandelic acid and homovanillic acid. When considered alongside established outcome predictors of coma, such as Glasgow coma scale and other clinical predictors (papillary light responses, corneal reflexes, motor responses to pain, myoclonus, status epilepticus), electroencephalogram, sensory evoked potentials, measurement of serum NSE concentrations provides additional information. Elevated levels are indicative of a poor outcome. Currently, no established algorithms exist to combine serum NSE concentrations and the various other predictors into a composite score that gives clear predictive outcome information. The NSE measurement therefore needs to be considered in a qualitative or semi-quantitative fashion and carefully weighed against other predictors by a physician experienced in examining and managing coma patients.

**Reference Values:**

< or =15 ng/mL

Serum markers are not specific for malignancy, and values may vary by method.

**Clinical References:**


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**Neuron-Specific Enolase (NSE), Spinal Fluid**

**Clinical Information:** Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron-specific enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF) are often elevated in diseases which result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum or CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jakob disease (CJD). NSE might also have utility as a prognostic marker in neuronal injury. There is, for example, increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, in particular when caused by hypoxic insult.

**Useful For:** An auxiliary test in the diagnosis of Creutzfeldt-Jakob disease. An auxiliary test in the diagnosis of small cell lung carcinoma metastasis to central nervous system or leptomeninges.
**Interpretation:** The diagnosis of Creutzfeldt-Jakob disease (CJD) is highly complex and involves clinical history and neurologic examination, detection of characteristic periodic sharp and slow wave complexes on electroencephalographs, magnetic resonance imaging (hyperintense basal ganglia), and exclusion of other possible causes of dementia, in addition to cerebrospinal fluid (CSF) examination. Consequently, patients are often diagnosed as having possible, probable, or definite CJD based upon the constellation of clinical findings. Detection of elevated CSF levels of NSE protein in these patients assists in the final diagnosis. A CSF neuron-specific enolase (NSE) within the normal reference range makes sporadic CJD very unlikely, but can be observed in less rapidly progressive forms of CJD, such as variant CJD related to infection with prions that cause bovine spongiform encephalopathy. With the previous Mayo Clinic-developed assay, in a group of carefully pre-selected patients with a probable diagnosis of CJD and an indeterminate or elevated NSE concentration in CSF, the respective diagnostic sensitivities of approximately 87% and approximately 80%, and diagnostic specificities of approximately 66% and approximately 83% were observed. Small cell lung carcinoma central nervous system metastases, particularly if they involve the leptomeninges, will lead to, usually substantial, elevations in CSF NSE concentrations.

**Reference Values:**
Normal: < or =15 ng/mL
Indeterminate: 15-30 ng/mL
Elevated: >30 ng/mL
Elevated results may indicate the need for additional work-up. Possible causes may be NSE-secreting central nervous system/leptomeningeal tumor or rapid neuronal destruction from a variety of causes. In the context of dementia, elevated results may be suggestive of Creutzfeldt-Jakob disease.

**Clinical References:**

**Neurotensin**

**Clinical Information:** Neurotensin is a 13 amino acid peptide produced primarily by endocrine cells of the ileal mucosa. Physiological actions of Neurotensin include hypertension, vasodilation, hyperglycemia, and inhibition of gastric motility. Its C-terminus is similar to Angiotensin I. It is a potent analgesic affecting hypothermia, muscle relaxation, and decreased motor activity. Pancreatic Polypeptide secretion is strongly stimulated by Neurotensin. Neurotensin appears to cause the release of Luteinizing Hormone-Releasing Hormone and Corticotropin Releasing Hormone effecting the release of Luteinizing Hormone, Follicle Stimulating Hormone, and ACTH but not Thyroid Stimulating Hormone or Growth Hormone. Neurotensin also stimulates pancreatic bicarbonate and intestinal secretion. Neurotensin levels are stimulated by food and Bombesin. Elevated levels have been found in pancreatic endocrine tumors, Oat Cell, Squamous, and Adeno Carcinomas. Elevated levels have been found to cause watery diarrhea.

**Reference Values:**
50 - 100 pg/mL.

**Neurotransmitter Metabolites/Amines**

**Interpretation:** Recently, a cerebral folate deficiency syndrome has been described. The clinical picture is one of developmental delay/regression, cerebellar ataxia, with or without seizures, with or without autism. This disorder is treatable with folic acid. If your patient fits the clinical picture we can
measure 5-methyltetrahydrofolate in the CSF we already have if you wish to add on this test. Please see: Ramaekers VT, Blau N. Cerebral folate deficiency, Dev Med Child Neurol. 2004 Dec;46(12):843-51. Cerebral folate deficiency has also been described in mitochondrial disorders. We now have biomarkers for folinic acid/pyridoxine responsive seizures (Antiquitin, ALDH7A1) that appear on our neurotransmitter metabolite chromatogram.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>3-O-MD (nmol/L)</th>
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<tbody>
<tr>
<td>0-0.2</td>
<td>208-1159</td>
<td>337-1299</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>179-711</td>
<td>450-1132</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>129-520</td>
<td>294-1115</td>
<td>&lt;300</td>
</tr>
<tr>
<td>2.0-5.0</td>
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<td>233-928</td>
<td>&lt;150</td>
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<tr>
<td>5.0-10</td>
<td>66-338</td>
<td>218-852</td>
<td>&lt;100</td>
</tr>
<tr>
<td>10-15</td>
<td>67-189</td>
<td>167-563</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Adults</td>
<td>67-140</td>
<td>145-324</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Interpretation performed by Keith Hyland, Ph.D.

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

**DISCLAIMER** required by the FDA for high complexity clinical laboratories: HPLC testing was developed and its performance characteristics determined by Medical Neurogenetics. These HPLC tests have not been cleared or approved by the U.S. FDA.

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**FNTSM 91940 Neurotransmitter Profile 3**

**Reference Values:**

5-Methyltetrahydrofolate

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5MTHF (nmol/L)</th>
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<td>2.0-5.0</td>
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<td>40-120</td>
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<td>40-120</td>
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Neurotransmitter Metabolites/Amines

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<th>Age (years)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>3-O-MD (nmol/L)</th>
</tr>
</thead>
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</tr>
<tr>
<td>Adults</td>
<td>67-140</td>
<td>145-324</td>
<td>&lt;100</td>
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Tetrahydrobiopterin/Neopterin Profile

<table>
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<th>Age (years)</th>
<th>BH4 (nmol/L)</th>
<th>Neop (nmol/L)</th>
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<td>0.2-0.5</td>
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<td>67-189</td>
</tr>
<tr>
<td>Adults</td>
<td>40-120</td>
<td>67-140</td>
</tr>
</tbody>
</table>
Newborn Aneuploidy Detection, FISH

**Clinical Information:** Approximately half of clinically recognizable spontaneous abortions have a major chromosomal anomaly. Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8/1,000 have a major chromosome anomaly, of which 6.5/1,000 involve aneuploidy of 1 of these 5 chromosomes. Diagnosis of chromosomal disorders can be performed by chromosome analysis of uncultured blood, standard chromosome study, and the technique utilizing FISH based on interphase cells. Standard chromosome analysis takes 3 to 10 days and analysis from uncultured newborn blood is often unsatisfactory and labor-intensive. FISH based methods facilitate rapid diagnosis of aneuploidy and may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes. This test does not detect chromosomal aneuploidies other than 13, 18, 21, X, and Y or any structural anomaly that does not result in gain of these chromosomes. Low levels of mosaicism involving chromosomes 13, 18, 21, X, or Y may not be detected by this assay.

**Useful For:** Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in newborn peripheral blood specimens

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Next Generation Sequencing (NGS), Acute Myeloid Leukemia

**Clinical Information:** Next-generation sequencing (NGS) is a rapidly evolving and complex methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can provide critical prognostic information and may help in guiding therapeutic management decisions by physicians.
Useful For: Evaluation of acute myeloid leukemia (AML) at the time of diagnosis, to assist in appropriate classification and prognosis. This test can be used at the time of relapsed AML to determine if a different gene mutation profile is present.

Interpretation: Mutations (gene alterations) identified, if present. An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

FNIAC
91379

Niacin (Vitamin B3)
Reference Values:
Units: ug/mL
Adult Reference Range:
> or = 10 years
Normal 0.50 â€“ 8.45
Low <0.50
High >8.45

Pediatric Reference Range:
<10 years
Normal 0.50 â€“ 8.91
Low <0.50
High >8.91

FNCGE
57888

Nickel Chloride IgE
Reference Values:
Class Conc IU/mL Interpretation
Neg <0.05 Negative
0/I 0.05 â€“ 0.08 Equivocal
I 0.08 â€“ 0.15 Positive
II 0.15 â€“ 0.50 with
III 0.50 â€“ 2.50 Increasing
IV 2.50 â€“ 12.50 Antibody
V 12.50 â€“ 62.50 Concentration
VI >62.50

NIU
8626

Nickel, 24 Hour, Urine
Clinical Information: Nickel (Ni) is a silvery white metal that is widely distributed in the earth’s crust. Nickel is essential for the catalytic activity of some plant and bacterial enzymes but its role in humans has not been defined. Elemental nickel may be essential for life at very low concentrations and is virtually nontoxic. Nickel is commonly used in industry. It is a pigment in glass, ceramics, and fabric.
Nickel, Random, Urine

Clinical Information: Nickel (Ni), a silvery white metal widely distributed in the earth's crust, is essential for the catalytic activity of some plant and bacterial enzymes, but its role in humans has not been defined. Elemental nickel may be essential for life at very low concentrations and is virtually nontoxic. Nickel is commonly used in industry. It is a pigment in glass, ceramics, and fabric dyes. It is converted in the Mond process to nickel carbonyl, Ni(CO)₄, and used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties) in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)₄, a liquid with low vapor pressure, is 1 of the most toxic chemicals known to man. Ni(CO)₄ is absorbed after inhalation, readily crosses all biological membranes, and noncompetitively inhibits ATP-ase and RNA polymerase. Breathing the vapors of Ni(CO)₄ binds avidly to hemoglobin with resultant inability to take up oxygen. The affinity for hemoglobin is higher than carbon monoxide. The binding to hemoglobin is the main transport mechanism for spreading Ni(CO)₄ throughout the body. Urine is the specimen of choice for the determination of nickel exposure via inhalation. Patients undergoing dialysis are exposed to nickel and accumulate nickel in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in nickel content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to nickel are localized skin sensitivity and allergic skin disorders that occur on contact with nickel-containing alloys. These reactions do not correlate to blood concentrations; patients experiencing skin sensitivity reactions to nickel are likely to have normal circulating concentrations of nickel.

Useful For: Detecting nickel toxicity in patients exposed to nickel carbonyl

Interpretation: Values > or = 7 mcg/24-hour specimen represent possible environmental or occupational exposure. Nickel concentrations > 50 mcg/24-hour specimen are of concern, suggesting excessive exposure. Clinical concern about nickel toxicity should be limited to patients with potential for exposure to toxic nickel compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of nickel, may be an incidental finding or could be due to specimen contamination.

Reference Values:
0.0-6.0 mcg/specimen
Reference values apply to all ages.

Clinical References:
to be no adverse health affects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

**Useful For:** Detecting nickel toxicity in patients exposed to nickel carbonyl

**Interpretation:** Values > or =7 mcg/L specimen represent possible environmental or occupational exposure. Nickel concentrations >50 mcg/L are of concern, suggesting excessive exposure. Clinical concern about nickel toxicity should be limited to patients with potential for exposure to toxic nickel compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of nickel, may be an incidental finding or could be due to specimen contamination.

**Reference Values:**

0.0-6.0 mcg/L

Reference values apply to all ages.

**Clinical References:**


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**NIS 8622**

**Clinical Information:** Nickel (Ni) is a silvery white metal that is widely distributed in the earth's crust. Nickel is essential for the catalytic activity of some plant and bacterial enzymes but its role in humans has not been defined. Elemental nickel may be essential for life at very low concentrations and is virtually nontoxic. Nickel is commonly used in industry. It is a pigment in glass, ceramics, and fabric dyes; is converted in the Mond process to nickel carbonyl, Ni(CO)₄, and used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties) in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)₄, a liquid with low vapor pressure, is 1 of the most toxic chemicals known to man. Ni(CO)₄ is absorbed after inhalation, readily crosses all biological membranes, and noncompetitively inhibits ATP-ase and RNA polymerase. When Ni(CO)₄ vapor is inhaled it binds avidly to hemoglobin with resultant inability to take up oxygen. The affinity for hemoglobin is higher than carbon monoxide. The binding to hemoglobin is the main transport mechanism for spreading Ni(CO)₄ throughout the body. Urine is the specimen of choice for the determination of nickel exposure via inhalation. Patients undergoing dialysis are exposed to nickel and accumulate nickel in blood and other organs; there appear to be no adverse health affects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in nickel content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to nickel are localized skin sensitivity and allergic skin disorders that occur on contact with nickel-containing alloys. These reactions do not correlate to blood concentrations; patients experiencing skin sensitivity reactions to nickel are likely to have normal circulating concentrations of nickel.

**Useful For:** Urine nickel is the test of choice for detecting nickel toxicity in patients exposed to nickel carbonyl

**Interpretation:** Values >2.0 ng/mL represent possible environmental or job-related exposure. Toxic concentrations are > or =10 ng/mL. Normal values are based on a Mayo Clinic study using healthy volunteers. Toxic values have been deduced from observation and unpublished internal study. Clinical concern about nickel toxicity should be limited to patients with potential for exposure to toxic nickel compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of nickel, may be an incidental finding or could be due to specimen contamination.
Reference Values:
< 2.0 ng/mL

Clinical References:

Nickel/Creatinine Ratio, Random, Urine

Clinical Information: Nickel (Ni), a silvery white metal widely distributed in the earth's crust, is essential for the catalytic activity of some plant and bacterial enzymes but its role in humans has not been defined. Elemental Ni may be essential for life at very low concentrations and is virtually nontoxic. Ni is commonly used in industry. It is a pigment in glass, ceramics and fabric dyes. It is converted in the Mond process to nickel carbonyl, Ni(CO)(4), and used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties) in Ni-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)(4) is very toxic. Ni(CO)(4), a liquid with low vapor pressure, is one of the most toxic chemicals known to man. Ni(CO)(4) is absorbed after inhalation, readily crosses all biological membranes, and noncompetitively inhibits ATP-ase and RNA polymerase. Ni(CO)(4) binds avidly to hemoglobin with resultant inability to take up oxygen. The affinity for hemoglobin is higher than carbon monoxide. The binding to hemoglobin is the main transport mechanism for spreading Ni(CO)(4) throughout the body. Urine is the specimen of choice for the determination of Ni exposure via inhalation. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in Ni content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to Ni are localized skin sensitivity and allergic skin disorders that occur on contact with Ni-containing alloys. These reactions do not correlate to urine concentrations; patients experiencing skin sensitivity reactions to Ni are likely to have normal Ni excretion.

Useful For: Urine nickel is the test of choice for detecting nickel toxicity in patients exposed to nickel carbonyl.

Interpretation: Values > or = 7 mcg/g creatinine represent possible environmental or occupational exposure. Nickel (Ni) concentrations > 50 mcg/g creatinine are of concern, suggesting excessive exposure. Clinical concern about Ni toxicity should be limited to patients with potential for exposure to toxic Ni compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of Ni, may be an incidental finding or could be due to specimen contamination.

Reference Values:
0.0-6.0 mcg/g creatinine
Reference values apply to all ages.

Clinical References:

Nicotine and Metabolites, Serum

Clinical Information: Tobacco use is the leading cause of death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting
substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of 2 hours. Cotinine exhibits an apparent elimination half-life of 15 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values <2.0 ng/mL and cotinine <2.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

**Useful For:** Monitoring tobacco use

**Interpretation:** Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using a tobacco product, see NICOU / Nicotine and Metabolites, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products indicates recent tobacco use. Typical findings are as follows: While using a tobacco product: -Peak nicotine concentration: 30 to 50 ng/mL -Peak cotinine concentration: 200 to 800 ng/mL* *Higher values may be seen in subjects with high cytochrome P450 2D6 activity Tobacco user after 2 weeks complete abstinence: -Nicotine concentration: <2.0 ng/mL -Cotinine concentration: <2.0 ng/mL Nontobacco user with passive exposure: -Nicotine concentration: <2.0 ng/mL -Cotinine concentration: <8.0 ng/mL Nontobacco user with no passive exposure: -Nicotine concentration: <2.0 ng/mL -Cotinine concentration: <2.0 ng/mL

**Reference Values:**

<table>
<thead>
<tr>
<th>NICOTINE</th>
<th>&lt;2.0 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>COTININE</td>
<td>&lt;2.0 ng/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**

receiving high-dose nicotine patch therapy. In addition to nicotine and metabolites, tobacco products also contain other alkaloids that can serve as unique markers of tobacco use. Two such markers are anabasine and nornicotine. Anabasine is present in tobacco products, but not nicotine replacement therapies. Nornicotine is present as an alkaloid in tobacco products and as a metabolite of nicotine. The presence of anabasine >10 ng/mL or nornicotine >30 ng/mL in urine indicates current tobacco use, irrespective of whether the subject is on nicotine replacement therapy. The presence of nornicotine without anabasine is consistent with use of nicotine replacement products. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit urine nicotine values <30 ng/mL, cotinine <50 ng/mL, anabasine <2 ng/mL, and nornicotine <2 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Urine cotinine has been observed to accumulate up to 20 ng/mL from passive exposure. Neither anabasine nor nornicotine accumulates from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in a random urine specimen to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate. Quantification of urine nicotine and metabolites while a patient is actively using a tobacco product is useful to define the concentrations that a patient achieves through self-administration of tobacco. Nicotine replacement dose can then be tailored to achieve the same concentrations early in treatment to assure adequate nicotine replacement so the patient may avoid the strong craving they may experience early in the withdrawal phase. This can be confirmed by measurement of urine nicotine and metabolite concentrations at steady-state (2-3 days after replacement therapy is started). Once the patient is stabilized on the dose necessary to achieve complete replacement and responding well to therapy, the replacement dose can be slowly tapered to achieve complete withdrawal.

**Useful For:** Monitoring tobacco use Monitoring patients on nicotine-replacement therapy for concurrent use of tobacco products

**Interpretation:** Urine nicotine in the range of 1,000 to 5,000 ng/mL with cotinine in the range of 1,000 to 8,000 ng/mL indicates the subject is either actively using a tobacco product or on high-dose nicotine patch therapy. The presence of anabasine and nornicotine indicates a subject on patch therapy who is actively using a tobacco product. Typical findings are as follows: While using a tobacco product: -Peak nicotine concentration: 1,000 to 5,000 ng/mL -Peak cotinine concentration: 1,000 to 8,000 ng/mL -Anabasine concentration: 10 to 500 ng/mL -Nornicotine concentration: 30 to 900 ng/mL Tobacco user after 2 weeks complete abstinence: -Nicotine concentration: <30 ng/mL -Cotinine concentration: <50 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL Nontobacco user with passive exposure: -Nicotine concentration: <20 ng/mL -Cotinine concentration: <20 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL Nontobacco user with no passive exposure: -Nicotine concentration: <2.0 ng/mL -Cotinine concentration: <5.0 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL

**Reference Values:**

- Non-tobacco user with no passive exposure:
  - NICOTINE <2.0 ng/mL
  - COTININE <5.0 ng/mL
  - ANABASINE <2.0 ng/mL
  - NORNICOTINE <2.0 ng/mL

Niemann-Pick Disease, Types A and B, Full Gene Analysis

Clinical Information: Niemann-Pick disease (types A and B) is an autosomal recessive lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is generally milder, though variable in its clinical presentation. Most type B patients do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are responsible for the clinical manifestations of Niemann-Pick disease types A and B. Although this disease is panethnic, it has a significantly higher frequency in individuals of Ashkenazi Jewish and Northern African descent. The carrier rate for type A in the Ashkenazi Jewish population is 1/90. There are 3 common mutations in the Ashkenazi Jewish population: L302P, R496L, and fsP330, which account for approximately 97% of mutant alleles in this population. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutant alleles in Gran Canaria Island. Targeted mutation analysis (NPABP / Niemann-Pick Disease, Types A and B, Mutation Analysis) for these 4 mutations is thought to detect 90% of the mutant alleles leading to acid sphingomyelinase deficiency. Full gene analysis of the SMPD1 gene should be utilized to detect private mutations in individuals with abnormal enzyme activity and 1 or no mutations detected by the panel of common mutations. NPABP / Niemann-Pick Disease, Types A and B, Mutation Analysis is also the recommended test for carrier screening. For diagnostic testing, SPHT / Sphingomyelinase, Fibroblasts or LDSBS / Lysosomal Disorders Screen, Blood Spot should be performed prior to targeted mutation analysis or full gene analysis.

Useful For: Confirmation of a diagnosis of Niemann-Pick disease type A or B Carrier screening in cases where there is a family history of Niemann-Pick disease type A or B, but disease-causing mutations have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Niemann-Pick Disease, Types A and B, Mutation Analysis

Clinical Information: Niemann-Pick disease (types A and B) is a lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is milder, though variable in its clinical presentation. Most type B patients do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are known to cause Niemann-Pick disease types A and B. The carrier rate for Niemann-pick type A in the Ashkenazi Jewish population is 1 in 90. There are 3 common mutations in the Ashkenazi Jewish population: L302P, R496L, and fsP330. The carrier detection rate for Niemann-Pick type A with these 3 mutations using this assay is approximately 97%. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutation alleles in Gran Canaria Island.
**Useful For:** Carrier testing of Niemann-Pick disease types A and B for individuals of Ashkenazi Jewish ancestry
Prenatal diagnosis of Niemann-Pick disease types A and B for at-risk pregnancies
Confirmation of suspected clinical diagnosis of Niemann-Pick disease types A and B in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

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**Niemann-Pick Type C Detection, Fibroblasts**

**Clinical Information:** Niemann-Pick disease type C (NPC1) is caused by a defect in cellular cholesterol trafficking that results in the accumulation of unesterified cholesterol in late endosomes/lysosomes. Age of onset is variable and ranges from the perinatal period to adulthood, and clinical presentation is also highly variable. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by mutations in either the NPC1 or NPC2 genes. About 95% of individuals with NPC have mutations in the NPC1 gene. Mutations may also be identified in the NPC2 gene; see NPCMS / Niemann-Pick Type C, Full Gene Analysis.

**Useful For:** Diagnosis of Niemann-Pick disease type C

**Interpretation:** Values expected in Niemann-Pick disease type C are <10% of that found in normal cultured fibroblasts. Values between 10% and 80% of normal will have to be judged on other diagnostic criteria. All values will be followed up by filipin staining for cholesterol.

**Reference Values:** If the results indicate that the patient's cultured fibroblasts esterify cholesterol at a level which is <10% of normal cultured fibroblasts and when filipin staining shows excessive storage of free cholesterol, it will be stated that the patient is positive for Niemann-Pick type C disease. All samples will be stained by filipin to see if a milder biochemical phenotype is the likely cause of the Niemann-Pick disease-like clinical picture.

**Clinical References:**
1. Online Mendelian Inheritance in Man (OMIM): entry 257220
Clinical Information: Niemann-Pick type C (NPC) is an inherited disorder of cholesterol transport that results in an accumulation of unesterified cholesterol and lipids in the lysosomal/endosomal system and in various tissues. Although NPC belongs to a group of lysosomal disorders including Niemann-Pick types A and B, these diseases are metabolically and genetically distinct. Niemann-Pick types A and B are caused by mutations in the SMPD1 gene, which encodes the enzyme sphingomyelinase, whereas NPC is caused by mutations in the NPC1 or NPC2 genes. The incidence of NPC is approximately 1 in 120,000 to 1 in 150,000 live births. Age of onset is variable and ranges from the perinatal period to adulthood. Clinical presentation is also highly variable. Infants may present with or without liver disease (hepatosplenomegaly) and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Adult-onset NPC is associated with a slower progression and is characterized by neurologic and psychiatric problems. NPC is inherited in an autosomal recessive manner, in which affected individuals carry 2 mutations in either the NPC1 or NPC2 gene. Most mutations are family specific, although there are 2 mutations in the NPC1 gene that are more common than others. The G992W mutation is common in the French Acadian population of Nova Scotia. The I1061T mutation is the most common mutation worldwide, and is seen in patients of Hispanic and Western European (United Kingdom and France) descent. Full gene sequencing and analysis for large deletions and duplications of the NPC1 and NPC2 genes detect less common disease-causing mutations. The recommended first-tier test to screen for NPC is a biochemical test measuring cholesterol esterification coupled with filipin staining on a fibroblast specimen, NIEM / Niemann-Pick Type C Detection, Fibroblasts. Molecular testing provides confirmation of a biochemical diagnosis or a basis for carrier testing of family members. Individuals with abnormal biochemical results are more likely to have 2 identifiable mutations by molecular testing.

Useful For: Second-tier test for confirming a biochemical diagnosis of Niemann-Pick type C (NPC). Carrier testing of individuals with a family history of NPC when an affected individual is not available for testing or disease-causing mutations have not been identified.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


FNIFE 91747 Nifedipine, Serum/Plasma

Reference Values: Reporting limit determined each analysis. The effective daily dosage: 30 â€“ 120 mg. Reported therapeutic serum range: 25 â€“ 200 ng/mL.

NITU 8586 Nitrogen, Total, 24 Hour, Urine

Clinical Information: Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine, however, fecal nitrogen can account for 30% to 50% of total
nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of the protein catabolism and, therefore, urine and fecal nitrogen may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

**Useful For:** Assessing nutritional status (protein malnutrition) Evaluating protein catabolism

**Interpretation:** Urinary nitrogen excretion levels within the normal range are indicative of adequate nutrition. Slightly abnormal excretion rates may be a result of moderate stress or complications such as infection or trauma. Significantly abnormal excretion rates may be associated with severe stress due to multiple trauma, head injury, sepsis, or extensive burns. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g nitrogen/24 hours.

**Reference Values:**
- <16 years: not established
- ≥16 years: 4-20 g/24 hours

**Clinical References:**
NMR LipoProfile w/IR Markers

Reference Values:

Low:
- Moderate: 1000 ìg/ìL 1299
- Borderline-High: 1300 ìg/ìL 1599
- High: 1600 ìg/ìL
- Very High: >2000 Lipids

LDL-C
0 ìg< 19 years 0 ìg< 109 mg/dL

>19 years 0 ìg< 99 mg/dL

Optimal:
- Above Optimal: 100 ìg< 129
- Borderline: 130 ìg< 159
- High: 160 ìg< 189
- Very High: >189

Comment: LDL-C is inaccurate if patient is non-fasting.

HDL-C >36 mg/dL

Triglycerides
- 0 ìg< 9 yrs: 0 ìg< 74 mg/dL
- 10 ìg< 19 yrs: 0 ìg< 89 mg/dL
- >19 years 0 ìg< 149 mg/dL

Total Cholesterol
0 ìg< 19 years: 100 ìg< 169 mg/dL

>19 years 100 ìg< 199 mg/dL

LDL and HDL Particles

HDL-P (Total) >or= 30.5 umol/L
Small LDL-P nmol/L
LDL Size >20.5 nm PARTICLE CONCENTRATION AND SIZE <--
Lower CVD Risk Higher CVD Risk--> LDL AND HDL
PARTICLES Percentile in Reference Population

HDL-P (total) High 75th 50th 25th Low
- >34.9 34.9 30.5 26.7

Small LDL-P Low 25th 50th 75th High
- 117 527 839 >839 LDL Size <--
- Large (Pattern A) -->
- Small (Pattern B) -->
Comment: Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account. These assays were developed and their performance characteristics determined by LipoScience. These assays not been cleared by the US Food and Drug Administration. The clinical utility of these laboratory values have not been fully established. Insulin Resistance and Diabetes Risk

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Upper Normal Limit</th>
<th>Low 25th 50th 75th High</th>
<th>Low 50th 25th High</th>
<th>Low 75th 25th High</th>
<th>Low 25th 75th High</th>
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</thead>
<tbody>
<tr>
<td>Large VLDL-P nmol/L</td>
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<tr>
<td>Small LDL-P nmol/L</td>
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<tr>
<td>Large HDL-P &gt;or = 4.8 umol/L</td>
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<tr>
<td>LDL Size &gt;20.58 nm</td>
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<td>HDL Size &gt;or= 9.2 nm</td>
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</tr>
</tbody>
</table>

Insulin Resistance Score LP-IR Score < or = 45
Comment: LP-IR Score is inaccurate if patient is non-fasting.

INSULIN RESISTANCE/DIABETES RISK MARKERS Insulin Resistant --> Percentile in Reference Population

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
The LP-IR score is a laboratory developed index that has been associated with insulin resistance and diabetes risk and should be used as one component of a physician's clinical assessment. Neither the LP-IR score nor the subclasses listed above have been cleared by the US Food and Drug Administration. Test Performed by: Lab-Corp Burlington 1447 York Court Burlington, NC 57215-2230

SSF1
87294

Nocardia Stain

Reference Values:
The laboratory will provide an interpretive report.
Reported as positive or negative.

NSIP
31769

Non-Seasonal Inhalant Allergen Profile

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<tr>
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<td>3.50-17.4</td>
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</tbody>
</table>

Clinical Information: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a mutation in approximately 75% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in 30% to 75% of families. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 mutations are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with RAF1 mutations, but rarely associated with PTPN11. A number of related disorders exist that have phenotypic overlap with NS and are caused by mutations in the same group of genes. PTPN11 and RAF1 mutations have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Mutations in BRAF, MAP2K1, MAP2K2, and KRAS have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with mutations in HRAS. Variation in SHOC2 has been associated with a distinctive phenotype involving features of Noonan syndrome and loose anagen hair. Genes included in the Noonan Syndrome and Related Disorders Multi-Gene Panel Gene Protein Inheritance Disease Association BRAF V-RAF murine sarcoma viral oncogene homolog b1 AD Noonan/CFC/Costello syndrome CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome KRAS V-KI-RAS Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC NRAS Neuroblastoma ras viral oncogene homolog AD Noonan syndrome PTPN11 Protein-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/LEOPARD syndrome RAF1 V-raf-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome SHOC2 Suppressor of clear, c. Elegans, homolog of AD Noonan-syndrome like with loose anagen hair SOS1 Son of sevenless, drosophila, homolog 1 AD
Noonan-syndrome like with loose anagen hair Abbreviations: Autosomal dominant (AD)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome or related disorders Establishing a diagnosis of a Noonan syndrome or related disorders, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying mutations within genes known to be associated with increased risk for disease features allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published ACMG recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.


Norovirus RNA, Qualitative Real-Time PCR
Reference Values:
Reference Range: Not Detected

Norovirus, EIA (Stool)
Reference Values:
Norovirus Antigen: Not Detected

A negative result does not exclude norovirus infection.
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
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</tr>
<tr>
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<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>


### NOTRP

**Nortriptyline, Serum**

**Clinical Information:** Nortriptyline is a tricyclic antidepressant used for treatment of endogenous depression. It also is a metabolite of the antidepressant amitriptyline. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage; amitriptyline is used when the side effect of mild sedation is desirable. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect; blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is > or =300 ng/mL, characterized by QRS widening leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to nortriptyline with serum levels of 70 to 170 ng/mL. Risk of toxicity is increased with nortriptyline levels > or =300 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLabs.com Page 1449
Therapeutic concentration: 70-170 ng/mL
Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


Notch3 DNA Sequencing Test
Reference Values:
A final report will be attached in MayoAccess.

NT-Pro B-Type Natriuretic Peptide (BNP), Serum
Clinical Information: B-type natriuretic peptide (brain natriuretic peptide: BNP) is a small, ringed peptide secreted by the heart to regulate blood pressure and fluid balance.(1) This peptide is stored in and secreted predominantly from membrane granules in the heart ventricles in a pro form (proBNP). Once released from the heart in response to ventricle volume expansion and/or pressure overload, the N-terminal (NT) piece of 76 amino acids (NT-proBNP) is rapidly cleaved by the enzymes corin and/or furin to release the active 32 amino acid peptide (BNP).(2) Both BNP and NT-proBNP are markers of atrial and ventricular distension due to increased intracardiac pressure. The New York Heart Association (NYHA) developed a 4-stage functional classification system for congestive heart failure (CHF) based on the severity of the symptoms. Studies have demonstrated that the measured concentrations of circulating BNP and/or NT-proBNP increase with the severity of CHF based on the NYHA classification.

Useful For: An aid in the diagnosis of congestive heart failure

Reference Values:
Males
< or =45 years: 10-51 pg/mL
46 years: 10-53 pg/mL
47 years: 10-55 pg/mL
48 years: 10-56 pg/mL
49 years: 10-58 pg/mL
50 years: 10-59 pg/mL
51 years: 10-61 pg/mL
52 years: 10-62 pg/mL
53 years: 10-64 pg/mL
54 years: 10-67 pg/mL
55 years: 10-68 pg/mL
56 years: 10-70 pg/mL
57 years: 10-71 pg/mL
58 years: 10-73 pg/mL
59 years: 10-76 pg/mL
60 years: 10-77 pg/mL
61 years: 10-79 pg/mL
62 years: 10-82 pg/mL
63 years: 10-83 pg/mL
64 years: 10-85 pg/mL
65 years: 10-88 pg/mL
66 years: 10-89 pg/mL
67 years: 10-92 pg/mL
68 years: 10-95 pg/mL
69 years: 10-97 pg/mL
70 years: 10-100 pg/mL
71 years: 10-103 pg/mL
72 years: 10-104 pg/mL
73 years: 10-107 pg/mL
74 years: 10-110 pg/mL
75 years: 10-113 pg/mL
76 years: 10-116 pg/mL
77 years: 10-119 pg/mL
78 years: 10-122 pg/mL
79 years: 10-125 pg/mL
80 years: 10-128 pg/mL
81 years: 10-131 pg/mL
82 years: 10-135 pg/mL
> or =83 years: 10-138 pg/mL

Females
< or =46 years: 10-140 pg/mL
47 years: 10-141 pg/mL
48 years: 10-144 pg/mL
49 years: 10-146 pg/mL
50 years: 10-149 pg/mL
51 years: 10-150 pg/mL
52 years: 10-152 pg/mL
53 years: 10-155 pg/mL
54 years: 10-157 pg/mL
55 years: 10-160 pg/mL
56 years: 10-162 pg/mL
57 years: 10-166 pg/mL
58 years: 10-168 pg/mL
59 years: 10-171 pg/mL
60 years: 10-173 pg/mL
61 years: 10-177 pg/mL
62 years: 10-179 pg/mL
63 years: 10-183 pg/mL
64 years: 10-185 pg/mL
65 years: 10-189 pg/mL
66 years: 10-193 pg/mL
67 years: 10-196 pg/mL
68 years: 10-199 pg/mL
69 years: 10-202 pg/mL
70 years: 10-206 pg/mL
71 years: 10-210 pg/mL
72 years: 10-214 pg/mL
73 years: 10-218 pg/mL
74 years: 10-222 pg/mL
75 years: 10-227 pg/mL
76 years: 10-230 pg/mL
77 years: 10-235 pg/mL
78 years: 10-239 pg/mL
79 years: 10-244 pg/mL
80 years: 10-248 pg/mL
81 years: 10-253 pg/mL
82 years: 10-258 pg/mL
> or =83 years: 10-263 pg/mL


**NTXPR**

**Clinical Information:** Human bone is continuously remodeled through a process of osteoclast-mediated bone formation and resorption. This process can be monitored by measuring serum and urine markers of bone formation and resorption. Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is cross-linked at the N- and C-terminal ends of the molecule. The amino acid sequences and orientation of the cross-linked alpha 2 N-telopeptide of type 1 collagen make it a specific marker of human bone resorption. N-terminal telopeptide (NTx) molecules are mobilized from bone by osteoclasts and subsequently excreted in the urine. Elevated levels of NTx indicate increased bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and during fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and of no diagnostic value. By contrast, abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget's disease, multiple myeloma, and bony metastases, as well as various congenital diseases of bone formation and remodeling can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover, usually without increase in bone turnover, is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption and formation markers.

**Useful For:**
1. An adjunct in the diagnosis of medical conditions associated with increased bone turnover
2. The differential diagnosis of osteomalacia versus osteoporosis
3. Identifying individuals with osteoporosis with elevated bone turnover and consequent increased risk for rapid disease progression
4. Prediction of bone densitometry response to antiresorptive therapy of osteoporosis
5. Monitoring and assessing effectiveness of therapy in patients treated for osteopenia, osteoporosis, Paget disease, or other disorders treated with antiresorptive therapy
6. An adjunct in monitoring response to other therapeutic intervention in diseases with increased bone turnover (eg, rickets, osteomalacia, hyperthyroidism)

**Indications 3 through 5 have been endorsed by the Negotiated Rulemaking Committee of HCFA and are therefore federally reimbursed.**

**Interpretation:** Elevated levels of N-terminal telopeptide (NTx) indicate increased bone resorption. Most patients with osteopenia or osteoporosis have low, but unbalanced, bone turnover, with bone resorption dominating over bone formation. While this may result in mild elevations in bone turnover markers in these patients, finding significantly elevated urine NTx levels is atypical. Therefore, if levels are substantially elevated above the young adult reference range (> 1.5- to 2-fold), the likelihood of coexisting osteomalacia, or of an alternative diagnosis as described in the Clinical Information section, should be considered. When alternative causes for elevated NTx have been excluded in an osteopenia/osteoporosis patient, the patient must be considered at increased risk for accelerated progression of osteopenia/osteoporosis. A 50% or greater reduction in this resorption marker 3 to 6 months after initiation of therapy indicates a probably adequate therapeutic response. The Negotiated Rulemaking Committee of HCFA also recommends: "Because of significant specimen to specimen collagen crosslink physiologic variability (15%-20%), current recommendations for appropriate utilization include: 1 or 2 baseline assays from specified urine collections on separate days; followed by a repeat assay about 3 months after starting antiresorptive therapy; followed by a repeat assay in 12 months; thereafter not more than annually, if medically necessary." Patients with diseases such as hyperthyroidism, which can be cured, should have a return of bone NTx levels to the reference range within 3 to 6 months after complete cure.

**Reference Values:**

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1452
All units are reported in nmol Bone Collagen Equivalents/mmol creatinine.

Males
<6 years: 576-1,763
6-13 years: 307-1,367
14-17 years: 102-1,048
> or =18 years: 21-66

Females
<6 years: 576-1,763
6-13 years: 307-1,367
14-17 years: 55-378
> or =18 years: 19-63

Values are based on Mayo in-house studies of 75 children and adolescents age 3.5 to 18.5 and >100 adults.


NPM1
Nucleophosmin (NPM1) Mutation Analysis

Clinical Information: Acute myelogenous leukemia (AML) is a heterogenous group of neoplasms. While cytogenetic aberrations detected at the time of diagnosis are the most commonly used prognostic feature, approximately 20% of AML cases show a normal karyotype, which is considered an intermediate-risk feature. Within this group, FLT3 mutations are considered indicators of poor prognosis. However, in the absence of a FLT3 mutation, the presence of a nucleophosmin (NPM1) mutation is associated with a more favorable prognosis. Thus, in patients with newly diagnosed AML, those with normal karyotype, no FLT3 mutation, and a NPM1 mutation are considered to have a better prognosis than patients in the same group with neoplasms lacking a NPM1 mutation.

Useful For: As a prognostic indicator in patients with newly diagnosed acute myelogenous leukemia with normal karyotype and no FLT3 mutation

Interpretation: The assay will be interpreted as positive, low positive, or negative for the NPM1 mutation. In patients with newly diagnosed acute myelogenous leukemia, a normal karyotype, and no FLT3 mutation, the presence of NPM1 mutation is an indicator of a more favorable prognosis.

Reference Values:
An interpretive report will be provided.


NMEG
Nutmeg, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
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<td>Strongly positive</td>
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<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages. (Class 0, IgE negative, and Class 6, IgE strongly positive apply to all ages.)


**NUTSP 31771**

**Nuts Allergen Profile**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or ≥100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*


**FNGPG 57930 Nuts and Grains Panel IgG**

**Reference Values:**

- Almond Food IgG
- Buckwheat IgG
- Corn IgG
- Gluten IgG
- Bean Kidney IgG
- Lentil IgG
- Bean Lima IgG
- Oat IgG
- Peanut IgG
- Pecan Food IgG
- Rice IgG
- Rye Food IgG
- Sesame Seed IgG
- Soybean IgG
- Sunflower IgG
- Walnut Food (Juglans spp) IgG

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Wheat IgG

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FOAKE 57999**

**Oak Live (Quercus virginiana) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**FROE 57907**

**Oak Red (Quercus rubra) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**OAK 82673**

**Oak, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


Oat IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200
Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Oat, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L  Interpretation
0                 Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


OCC2
81870

Occupational Panel # 2

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0                 Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive

Octopus, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Oil Red O Stain (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**Olanzapine (Zyprexa)**

**Reference Values:**

Reference Range: 10.0 – 80.0 ng/mL

Expected steady state concentrations in patients on recommended daily dosages:

- Plasma concentrations of olanzapine greater than 9.0 ng/mL have been associated with therapeutic effect.

Toxic range has not been established.

**Oligoclonal Banding, Serum and Spinal Fluid**

**Clinical Information:** The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the cerebrospinal fluid (CSF) IgG index and CSF oligoclonal band (OCB) detection. Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of MS patients. At least 1 of these tests has been reported to be positive in 90% of MS patients when both test are performed. Newer methodologies for OCB detection have been reported to be more sensitive, with sensitivities of 90% to 95% in CSF from MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases and, therefore, this assay is not specific for MS (specificity = 95%).

**Useful For:** Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings

**Interpretation:** A finding of 4 or more cerebrospinal fluid (CSF)-specific bands (ie, bands that are present in CSF but are absent in serum) is consistent with multiple sclerosis. The presence of oligoclonal band is unrelated to disease activity.

**Reference Values:**

CSF Olig Bands Interpretation: <4 bands

**Clinical References:**


**Oligosaccharidoses Screen, Fibroblasts**

**Clinical Information:** Oligosaccharidoses are a group of autosomal recessively inherited lysosomal disorders of glycoprotein catabolism. There is no treatment available at this time for these disorders. Details about the different oligosaccharidoses detected by this screening test are provided in the Table.

**Table. Conditions identifiable by method(1):**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Onset</th>
<th>Gene</th>
<th>Enzyme</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-mannosidosis</td>
<td>Infant (severe, Type I)</td>
<td>MAN2B1</td>
<td>Mannosidase (alpha-Mann)</td>
<td>1:500,000</td>
</tr>
<tr>
<td>Beta-mannosidosis</td>
<td>Infant (severe, Type II)</td>
<td>MANBA</td>
<td>Mannosidase (beta-Mann)</td>
<td>&lt;30 patients</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
highly variable; learning difficulties, deafness, frequent infections
Alpha-fucosidosis Infancy to early childhood FUCA1 Alpha-fucosidase (alpha-Fuc) <100 patients described Phenotype: highly variable; psychomotor retardation, coarse facial features, growth delay; angiokertoma, elevated sweat chloride
Schindler disease Infancy (severe, Type I; intermediate, Type III) Adult (mild, Type II) NAGA Alpha-N-Acetyl-galactosaminidase (alpha-NAcGal) <30 patients described Phenotype: highly variable; early onset neurodegenerative phenotype to late onset angiokeratoma to no symptoms (phenotype may be dependent on additional factors than just alpha-NAcGal deficiency
GM1 gangliosidosis (a sphingolipidosis) Infancy (severe, Type I; intermediate, Type II) Adult (mild, Type III) GLB1 Beta-galactosidase (beta-Gal) 1:200,000 Phenotype: fetal hydrops/neonatal cardiomyopathy to early developmental delay/arrest, facial coarseness, hepatosplenomegaly, failure to thrive, to 2nd/3rd decade onset of ataxia, speech abnormalities leading to spinocerebellar degeneration and cognitive decline.
Cherry-red spot in early onset variants Mucopolysaccharidosis type IVB (Morquio B) Childhood GLB1 Beta-galactosidase (beta-Gal) <30 patients described Phenotype: dwarfism with scoliosis and vertebral deformities noted between 1 and 4 years old and progressively worsening; typically no CNS involvement; keratan sulfate excretion in urine Sialidosis (ML I) Early adulthood (Type I) Earlier for congenital, infantile, and juvenile forms (Type II) NEU1 Alpha-neuraminidase (Neu) <30 patients described Phenotype: fetal hydrops to early developmental delay, coarse facial features, dysostosis multiplex and hepatosplenomegaly, to late onset cherry-red spot myoclonus syndrome Galactosialidosis Early infancy, late infancy or early adult CTSA Cathepsin A causing secondary deficiencies in beta-Gal and Neu <30 patients described Phenotype: highly variable from fetal hydrops, edema, coarse facial features, corneal clouding, cherry-red spot, dysostosis multiplex, hepatosplenomegaly, mental retardation to milder presentation with survival to adulthood Mucolipidosis II-alpha/-beta (I-Cell) Mucolipidosis III-alpha/-beta and III-gamma (Pseudo-Hurler Polydystrophy) Early infancy; death usually by age 5-8 GNPTAB N-acetylglucosaminyl-1-phosphotransferase deficiency causing secondary intracellular deficiency of multiple enzyme activities 1:300,000 Early childhood, may live well into adulthood Phenotype: Hurlerlike, with ML II being more severe and including cardiomyopathy and coronary artery disease

Useful For: Screening for possible oligosaccharidoses

Interpretation: This is a screening test; not all oligosaccharidoses are detected. The resulting enzyme activities may be characteristic of a specific disorder; however, abnormal results require confirmation by additional biochemical or molecular genetic analysis. When abnormal results are detected, a detailed interpretation is given, including an overview of results and significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional confirmatory studies (enzyme assay, molecular genetic analysis).

Reference Values:
An interpretive report will be provided.

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hepatosplenomegaly, mental retardation to milder presentation with survival to adulthood Mucolipidosis
II-alpha/-beta (I-Cell) Mucolipidosis III-alpha/-beta and III-gamma (Pseudo-Hurler Polydystrophy) Early
infancy; death usually by age 5 to 8 GNPTAB N-acetylglucosaminyl-1-phosphotransferase deficiency
causing secondary intracellular deficiency of multiple enzyme activities 1:300,000 Early childhood, may
live well into adulthood Phenotype: Hurler-like, with mucolipidosis II being more severe and including
cardiomyopathy and coronary artery disease

**Useful For:** Screening for possible oligosaccharidoses

**Interpretation:** This is a screening test; not all oligosaccharidoses are detected. The resulting enzyme
activities may be characteristic of a specific disorder; however, abnormal results require confirmation by
additional biochemical or molecular genetic analysis. When abnormal results are detected, a detailed
interpretation is given, including an overview of results and significance, a correlation to available clinical
information, elements of differential diagnosis, and recommendations for additional confirmatory studies
(enzyme assay, molecular genetic analysis).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** Part 16. In Scriver's The Online Metabolic and Molecular Bases of Inherited
Medical. Available at: http://www.ommbid.com/

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**FOLBG**

**Olive Black IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility
of food-specific IgG tests has not been established. These tests can be used in special clinical situations to
select foods for evaluation by diet elimination and challenge in patients who have food-related
complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as
evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.
This test should only be ordered by physicians who recognize the limitations of the test.

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**FOLRE**

**Olive Russian (Elaeagnus angustifolia) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69
Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 17.5 - 49.9 50.0 - 99.9 > or =
OLIV
82733

**Olive Tree, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


OLIVF
86306

**Olive-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
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**Reference values apply to all ages.**


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**NGSHM 63367 OncoHeme Next Generation Sequencing (NGS), Hematologic Neoplasms**

**Clinical Information:** Next-generation sequencing (NGS) is a rapidly evolving and complex methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many myeloid neoplasms lack a clonal cytogenetic finding at diagnosis (normal karyotype) but can be diagnosed and classified according to the gene mutation profile. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and sometimes therapeutic information for the managing physicians.

**Useful For:** Evaluation of hematologic neoplasms at the time of diagnosis, to assist in appropriate classification and prognosis Determine the presence of new clinically important gene mutation changes at relapse

**Interpretation:** Mutations (gene alterations) identified, if present. An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.
**Clinical References:**

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**Onion IgG**

**Interpretation:**
mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Onion, IgE**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:**
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**Interpretation:**
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<td>3.50-17.4</td>
<td>Positive</td>
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</table>
Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Codeine by LC-MS/MS: 50 ng/mL
Hydrocodone by LC-MS/MS: 50 ng/mL
Hydromorphone by LC-MS/MS: 50 ng/mL
Morphine by LC-MS/MS: 50 ng/mL
Oxycodone by LC-MS/MS: 50 ng/mL
Oxymorphone by LC-MS/MS: 50 ng/mL

Clinical References:

Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds(1): -Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect.(2) Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation. -Morphine is an opioid receptor agonist that is used for major pain analgesia.(2) It has been shown to distribute widely into many fetal tissues,(4) and has been detected in meconium. -Hydrocodone is a semisynthetic analgesic derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain.(2) -Hydromorphone, a semisynthetic derivative of morphine, is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine.(2) -Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphone.(2) -Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain.(2) -Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monooctylmorphine (6-MAM), which is further hydrolyzed to morphine.(2) Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of
pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Detection of maternal prenatal opiate/opioid use up to 5 months before birth

**Interpretation:** The presence of any of the following opiates (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) at > or =50 ng/g or 6-monoacetlymorphine at > or =10 ng/g indicates the newborn was exposed to opiates/opioids during gestation.

**Reference Values:**
Negative
Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**
- Codeine by LC-MS/MS: 50 ng/g
- Hydrocodone by LC-MS/MS: 50 ng/g
- Hydromorphone by LC-MS/MS: 50 ng/g
- Morphine by LC-MS/MS: 50 ng/g
- Oxycodone by LC-MS/MS: 50 ng/g
- Oxymorphone by LC-MS/MS: 50 ng/g

**Clinical References:**

**OPATX**

**Opiates Confirmation, Chain of Custody, Urine**

**Clinical Information:** Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours; and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the 6-beta-hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone, therefore the presence of hydromorphone could also indicate exposure to hydrocodone. Oxycodone is metabolized to noroxycodone, oxymorphone and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for the opiates is...
generally 2 to 3 days after last ingestion. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, and oxymorphone in urine. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**
Negative
Cutoff concentrations

**IMMUNOASSAY SCREEN**

<300 ng/mL

- Codeine by LC-MS/MS: <100 ng/mL
- Hydrocodone by LC-MS/MS: <100 ng/mL
- Hydromorphone by LC-MS/MS: <100 ng/mL
- Oxycodone by LC-MS/MS: <100 ng/mL
- Oxymorphone by LC-MS/MS: <100 ng/mL
- Morphine by LC-MS/MS: <100 ng/mL

**Clinical References:**
oxycodone. The detection interval for the opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, and oxymorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

- **Negative**
  - Cutoff concentrations
    - Codeine by LC-MS/MS: <100 ng/mL
    - Hydrocodone by LC-MS/MS: <100 ng/mL
    - Hydromorphone by LC-MS/MS: <100 ng/mL
    - Oxycodone by LC-MS/MS: <100 ng/mL
    - Oxymorphone by LC-MS/MS: <100 ng/mL
    - Morphine by LC-MS/MS: <100 ng/mL

**Clinical References:**


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**FOPIA 75030 Opiates, Serum or Plasma, Quantitative**

**Interpretation:** Identification of specific drug(s) taken by specimen donor is problematic due to common metabolites, some of which are prescription drugs themselves. The absence of expected drug(s) and/or drug metabolite(s) may indicate non-compliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, or limitations of testing. The concentration value must be greater than or equal to the cutoff to be reported as positive. A very small amount of an unexpected drug analyte in the presence of a large amount of an expected drug analyte may reflect pharmaceutical impurity. Interpretive questions should be directed to the laboratory.

**Reference Values:**

- Drugs covered: codeine, morphine, 6-acetylmorphine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. All drugs covered and the non-glucuronidated (free) form.

  - Positive cutoff: 2 ng/mL

For medical purposes only; not valid for forensic use.

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**OPRM1 89612 Opioid Receptor, Mu 1 (OPRM1) Genotype for Naltrexone Efficacy**

**Clinical Information:** The mu-opioid receptor (OPRM1) is the primary binding site of action for many opioid drugs and for binding of beta-endorphins. One of the effects of opiate and alcohol use is to increase release of beta-endorphins, which subsequently increases release of dopamine and stimulates cravings. Naltrexone is an opioid antagonist used to treat abuse of opiates, alcohol, and other substances. Naltrexone binds to OPRM1, preventing beta-endorphin binding and subsequently reducing the craving for substances of abuse.(1) The A355G polymorphism (rs1799971) in exon 1 of the OPRM1 gene (OPRM1) results in an amino acid change, Asn102Asp. Historically, this mutation has been referred to in the literature as 118A->G (Asn40Asp).(2) The G allele leads to loss of the putative N-glycosylation site in the extracellular receptor region, causing a decrease in OPRM1 mRNA and protein levels, but a 3-fold increase in beta-endorphin binding at the receptor.(3) Studies have shown individuals who carry at least 1 G allele have significantly better outcomes with naltrexone therapy including lower rate of relapse (P=0.044), a longer time to return to heavy drinking, and <20% relapse rate after 12 weeks of treatment.
compared with individuals who are homozygous for the A allele (55% relapse rate).(4) Other studies indicated that 87.1% of G allele carriers had a good clinical outcome, compared with only 54.8% of individuals with the A/A genotype (odds ratio, 5.75; confidence interval, 1.88-17.54).(1) A haplotype-based approach confirmed that the single OPRM1 355A->G locus was predictive of response to naltrexone treatment. (1) Frequency of the 355G allele varies with ethnicity but ranges between 10% and 40% (European 20%, Asian 40%, African American 10%, and Hispanic 25%).

**Useful For:** Identifying individuals with a higher probability of successful treatment for alcoholism with naltrexone

**Interpretation:** An interpretative report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**Opioid Receptor, Mu 1 (OPRM1) Genotype for Naltrexone Efficacy, Saliva**

**Clinical Information:** The mu-opioid receptor (OPRM1) is the primary binding site of action for many opioid drugs and for binding of beta-endorphins. One of the effects of opiate and alcohol use is to increase release of beta-endorphins, which subsequently increases release of dopamine and stimulates cravings. Naltrexone is an opioid antagonist used to treat abuse of opiates, alcohol, and other substances. Naltrexone binds to OPRM1, preventing beta-endorphin binding and subsequently reducing the craving for substances of abuse. (1) The A355G polymorphism (rs1799971) in exon 1 of the OPRM1 gene (OPRM1) results in an amino acid change, Asn102Asp. Historically, this mutation has been referred to in the literature as 118A->G (Asn40Asp). (2) The G allele leads to loss of the putative N-glycosylation site in the extracellular receptor region, causing a decrease in OPRM1 mRNA and protein levels, but a 3-fold increase in beta-endorphin binding at the receptor. (3) Studies have shown individuals who carry at least 1 G allele have significantly better outcomes with naltrexone therapy including lower rate of relapse (P=0.044), a longer time to return to heavy drinking, and <20% relapse rate after 12 weeks of treatment compared with individuals who are homozygous for the A allele (55% relapse rate). (4) Other studies indicated that 87.1% of G allele carriers had a good clinical outcome, compared with only 54.8% of individuals with the A/A genotype (odds ratio, 5.75; confidence interval, 1.88-17.54). (1) A haplotype-based approach confirmed that the single OPRM1 355A->G locus was predictive of response to naltrexone treatment. (1) Frequency of the 355G allele varies with ethnicity but ranges between 10% and 40% (European 20%, Asian 40%, African American 10%, and Hispanic 25%).

**Useful For:** Identifying individuals with a higher probability of successful treatment for alcoholism with naltrexone

**Interpretation:** An interpretative report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**FORNG**

**Orange IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FORE**

**Orange Roughy IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive Very High Positive Very High Positive Very High Positive

**Reference Values:**

<0.35 kU/L

**ORNG**

**Orange, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class IgE kU/L Interpretation

0 Negative
ORCH
82907

**Orchard Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Oregano IgG

**Interpretation:** mcg/mL of IgG
Lower Limit of Quantitation 2.0
Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Oregano, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.
Organic Acids Screen, Urine

Clinical Information: Organic acids occur as physiologic intermediates in a variety of metabolic pathways. Organic acidurias are a group of disorders in which one or more of these pathways are blocked, resulting in a deficiency of normal products and an abnormal accumulation of intermediate metabolites (organic acids) in the body. These excess metabolites are excreted in the urine. The incidence of individual inborn errors of organic acid metabolism varies from 1 in 10,000 to >1 in 1,000,000 live births. Collectively, their incidence approximates 1 in 3,000 live births. This estimate, however, does not include other inborn errors of metabolism (ie, amino acid disorders, urea cycle disorders, congenital lactic acidemias) for which diagnosis and monitoring may also require organic acid analysis. All possible disease entities included, the incidence of conditions where informative organic acid profiles could be detected in urine is likely to approach 1 in 1,000 live births. Organic acidurias typically present with either an acute life-threatening illness in early infancy or unexplained developmental delay with intercurrent episodes of metabolic decompensations in later childhood. A situation of severe and persistent metabolic acidosis of unexplained origin, elevated anion gap, and severe neurologic manifestations, such as seizures, should be considered strong diagnostic indicators of one of these diseases. The presence of ketonuria, occasionally massive, provides an important clue toward the recognition of disorders, especially in the neonatal period. Hyperammonemia, hypoglycemia, and lactic acidemia are frequent findings, especially during acute episodes of metabolic decompensations.

Useful For: Diagnosis of inborn errors of metabolism

Interpretation: When no significant abnormalities are detected, the organic acid analysis is reported and interpreted in qualitative terms only. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis).

Reference Values: An interpretive report will be provided.

**ANIDE 8114**

**Organism Referred for Identification, Anaerobic Bacteria**

**Clinical Information:** Anaerobic bacteria are the greatest component of the human body's normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts. Their presence is important in promoting vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. Anaerobes generally are of low pathogenicity, but may possess virulence factors such as endotoxin or polysaccharide capsules or produce extracellular toxins. Disease occurs when a large inoculum develops in an area lacking oxygen or with a poor blood supply. Typical anaerobic infections include peritonitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema, lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Many Bacteroides produce beta-lactamase and are resistant to penicillins and cephalosporins. Imipenem, metronidazole, and clindamycin are effective agents, although resistance to clindamycin is increasing.

**Useful For:** Identification of anaerobic bacteria involved in human infections

**Interpretation:** Isolation of anaerobes in significant numbers from well-collected specimens from blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with the identified organism.

**Reference Values:**
Identification of organism

**Clinical References:**

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**OROT 8905**

**Orotic Acid, Urine**

**Clinical Information:** The urinary excretion of orotic acid, an intermediate in pyrimidine biosynthesis, is increased in many urea cycle disorders and in a number of other disorders involving the metabolism of arginine. The determination of orotic acid can be useful to distinguish between various causes of elevated ammonia (hyperammonemia). Hyperammonemia is characteristic of all urea cycle disorders, but orotic acid is elevated in only some, including ornithine transcarbamylase deficiency, citrullinemia, and argininosuccinic aciduria. Orotic acid is also elevated in the transport defects of dibasic amino acids (lysinuric protein intolerance and hyperornithinemia, hyperammonemia, and homocitrullinuria [HHH] syndrome), and greatly elevated in patients with hereditary orotic aciduria (uridine monophosphate synthase [UMPS] deficiency). Ornithine transcarbamylase (OTC) deficiency is an X-linked urea cycle disorder that affects both males and females due to random X-inactivation. It is thought to be the most common urea cycle disorder with an estimated incidence of 1:56,000. In OTC deficiency, carbamoyl phosphate accumulates and is alternatively metabolized to orotic acid. Allopurinol inhibits orotidine monophosphate decarboxylase and, when given to OTC carriers (who may have normal orotic acid excretion), can cause increased excretion of orotic acid. A carefully monitored allopurinol challenge followed by several determinations of a patient's orotic acid excretion can be useful to identify OTC carriers, as approximately 20% of OTC mutations are not detectable by current molecular genetic testing methods.

**Useful For:** Evaluation of the differential diagnosis of hyperammonemia and hereditary orotic aciduria When orotic acid is measured after a protein load or administration of allopurinol, excretion of orotic acid is a very sensitive indicator of ornithine transcarbamylase (OTC) activity. An allopurinol challenge may
be helpful in determining whether a female patient may be a carrier of an OTC mutation if molecular genetic testing was not informative.

**Interpretation:** The value for the orotic acid concentration is reported. The interpretation of the result must be correlated with clinical and other laboratory findings.

**Reference Values:**

- <2 weeks: 1.4-5.3 mmol/mol creatinine
- 2 weeks-1 year: 1.0-3.2 mmol/mol creatinine
- 2-10 years: 0.5-3.3 mmol/mol creatinine
- > or =11 years: 0.4-1.2 mmol/mol creatinine

**Clinical References:**
Reference values have not been established for patients >83 years of age.


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**Osmolality, Body Fluid**

**Clinical Information:** Osmolality is an index of the solute concentration. It is determined by the number and not by the nature of the particles in solution. Dissolved solutes change the physical properties of solutions; they increase the osmotic pressure and decrease freezing point. Body fluids have the same osmolality as a corresponding serum specimen taken at the same time. "True body fluids" include: ascitic, cerebrospinal, hydrocele, edema, pericardial, pleural, spermatocoele and synovial fluids. Secretions not in equilibrium with the extra-cellular fluids of the body include gastric juice, saliva and sweat. Serum osmolality is normally between 275 to 295 mOsm/kg; it increases with dehydration and decreases with overhydration. Urine osmolality reflects the ability of the kidney to maintain tonicity and water balance. The normal kidney can concentrate urine to 800 to 1,400 mOsm/kg, and with excess fluid intake, a minimal osmolality of 40 to 80 mOsm/kg can be obtained.

**Useful For:** Determining the source and type of fluid

**Interpretation:** No normals are available.

**Reference Values:** No established reference values


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**Osmolality, Serum**

**Clinical Information:** Osmolality is a measure of the number of dissolved solute particles in solution. It is determined by the number and not by the nature of the particles in solution. Dissolved solutes change the physical properties of solutions, increasing the osmotic pressure and boiling point and decreasing the vapor pressure and freezing point. The osmolality of serum increases with dehydration and decreases with overhydration. The patient receiving intravenous fluids should have a normal osmolality. If the osmolality rises, the fluids contain relatively more electrolytes than water. If the osmolality falls, relatively more water than electrolytes is being administered. Normally, the ratio of serum sodium, in mEq/L, to serum osmolality, in mOsm/kg, is between 0.43 and 0.5. The ratio may be distorted in drug intoxication. Generally, the same conditions that decrease or increase the serum sodium concentration affect the osmolality. A comparison of measured and calculated serum osmolality produces a delta-osmolality. If this is >40 mOsm/kg a H2O in a critically ill patient, the prognosis is poor. An easy formula to calculate osmolality is: Osmolality (mOsm/kg H2O)=2 Na+ Glucose + BUN 20 3

**Useful For:** Evaluating acutely ill or comatose patients

**Interpretation:** An increased gap between measured and calculated osmolality may indicate ingestion of poison, ethylene glycol, methanol, or isopropanol.

**Reference Values:** 275-295 mOsm/kg

**Clinical References:** Murphy JE, Henry JB: Evaluation of renal function, and water, and electrolyte,
Osmolality, Urine

Clinical Information: Osmolality is an index of the solute concentration. Urine osmolality is a measure of the concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts in urine. Urinary osmolality corresponds to urine specific gravity in nondisease states. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine either routinely or under artificial conditions. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality and if urine electrolyte studies are performed. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality.

Useful For: Assessing the concentrating and diluting ability of the kidney

Interpretation: With normal fluid intake and normal diet, a patient will produce a urine of about 500 to 850 mosmol/kg water. Above age of 20 years there is an age dependent decline in the upper reference range of approximately 5 mOsm/kg/year. The normal kidney can concentrate a urine to 800 to 1,400 mosmol/kg and with excess fluid intake, a minimal osmolality of 40 to 80 mosmol/kg can be obtained. With dehydration, the urine osmolality should be 3 to 4 times the plasma osmolality.

Reference Values:
0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg


Osmotic Fragility, Erythrocytes

Clinical Information: Spherocytes are osmotically fragile cells that rupture more easily in a hypotonic solution than do normal RBCs. Because they have a low surface area:volume ratio, they lyse at a higher osmolarity than do normal discocyte (RBCs). Cells that have a larger surface area:volume ratio, such as target cells or hypochromic cells are more resistant to lysing. After incubation, an increase in hemolysis is seen in spherocytes. Hereditary spherocytosis typically has greater number of spherocytes than other causes of spherocytosis. Therefore, the degree of lysis is usually more pronounced, but this is not always the case. Some rare disorders can also cause marked fragility and hereditary spherocytosis cases can display moderate fragility.

Useful For: Evaluation of suspected hereditary spherocytosis associated hemolytic anemia Confiming or detecting mild spherocytosis

Interpretation: An interpretive report will be provided.

Reference Values:
> or =12 months:
0.50 g/dL NaCl (unincubated): 3-53% hemolysis
0.60 g/dL NaCl (incubated): 14-74% hemolysis
0.65 g/dL NaCl (incubated): 4-40% hemolysis
0.75 g/dL NaCl (incubated): 1-11% hemolysis

Reference values have not been established for patients who are <12 months of age.

Osteocalcin, Serum

**Clinical Information:** Osteocalcin, the most important noncollagen protein in bone matrix, accounts for approximately 1% of the total protein in human bone. It is a 49-amino acid protein with a molecular weight of approximately 5800 daltons. Osteocalcin contains up to 3 gamma-carboxyglutamic acid residues as a result of posttranslational, vitamin K-dependent enzymatic carboxylation. Its production is dependent upon vitamin K and is stimulated by 1,25 dihydroxy vitamin D. Osteocalcin is produced by osteoblasts and is widely accepted as a marker of bone osteoblastic activity. Osteocalcin, incorporated into the bone matrix, is released into the circulation from the matrix during bone resorption and, hence, is considered a marker of bone turnover, rather than a specific marker of bone formation. Osteocalcin levels are increased in metabolic bone diseases with increased bone or osteoid formation including osteoporosis, osteomalacia, rickets, hyperparathyroidism, renal osteodystrophy, thyrotoxicosis, and in individuals with fractures, acromegaly, and bone metastasis. By means of osteocalcin measurements, it is possible to monitor therapy with antiresorptive agents (bisphosphonates or hormone replacement therapy [HRT]) in, for example, patients with osteoporosis or hyper-calcemia.(1) Decrease in osteocalcin is also observed in some disorders (eg, hypoparathyroidism, hypothyroidism, and growth hormone deficiency). Immunochemical and chromatographic studies have demonstrated considerable heterogeneity for concentrations of circulating osteocalcin in normal individuals and in patients with osteoporosis, chronic renal failure, and Pagetâ€™s disease. Both intact osteocalcin (amino acids 1-49) and the large N-terminal/midregion (N-MID) fragment (amino acids 1-43) are present in blood. Intact osteocalcin is unstable due to protease cleavage between amino acids 43 and 44. The N-MID-fragment, resulting from cleavage, is considerably more stable. This assay detects both the stable N-MID-fragment and intact osteocalcin.

**Useful For:** Monitoring and assessing effectiveness of antiresorptive therapy in patients treated for osteopenia, osteoporosis, Paget’s disease, or other disorders in which osteocalcin levels are elevated. As an adjunct in the diagnosis of medical conditions associated with increased bone turnover, including Paget’s disease, cancer accompanied by bone metastases, primary hyperparathyroidism, and renal osteodystrophy.

**Interpretation:** Elevated levels of osteocalcin indicate increased bone turnover. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy), a decrease of > or =20% from baseline osteocalcin level (ie, prior to the start of therapy) after 3 to 6 months of therapy, suggests effective response to treatment.(2) Patients with diseases such as hyperparathyroidism, which can be cured, should have a return of osteocalcin levels to the reference range within 3 to 6 months after complete cure.(3)

**Reference Values:**
- <18 years: not established
- > or =18 years: 9-42 ng/mL


Ovalbumin, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for...
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Ovomucoid, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
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</tbody>
</table>


**Ox-Eye Daisy, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Oxalate Analysis in Hemodialysate

**Clinical Information:** Oxalate is a dicarboxylic acid, an end product of glyoxalate and glycerate metabolism that is excreted in the urine where it is a common component of kidney stones (up to 85%). Hyperoxaluria can be either genetic (eg, primary hyperoxaluria) or acquired/secondary (eg, enteric hyperoxaluria), and can lead to nephrocalcinosis and renal failure. Monitoring the adequacy of oxalate removal during hemodialysis can be useful in the management of patients with hyperoxaluria and renal failure, particularly following transplantation.

**Useful For:** Determining the amount of oxalate removed during a dialysis session Individualizing the dialysis prescription of hyperoxaluric patients

**Interpretation:** A steady decrease in oxalate signal is expected through dialysis procedure. Signals below 2 mcM should be considered ideal conditions. Total oxalate removed during a dialysis session can be estimated by multiplying the concentration of oxalate in the dialysate by the oxalate flow rate for each time period that the oxalate is measured.

**Reference Values:** Not applicable

**Clinical References:**

Oxalate, 24 Hour, Urine

**Clinical Information:** Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate, so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

**Useful For:** Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

**Interpretation:** An elevated urine oxalate (>0.46 mmol/24 hours) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glycercic dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation.
Reference Values:
0.11-0.46 mmol/24 hours
9.7-40.5 mg/24 hours
The reference value is for a 24-hour collection. Specimens collected for other than a 24-hour time period are reported in unit of mmol/L for which reference values are not established.


Oxalate, Pediatric, Random, Urine

Clinical Information: Oxalate is an end product of glyoxylate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate, so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

Useful For: Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children. Therefore, this random test is offered for children <16 years old.

Interpretation: An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from <0.35 mmol/mL at birth to <0.15 mmol/mL at 1 year to <0.10 mmol/mL at 10 years and <0.05 mmol/mL at 20 years of age (see table below).(1)

Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048

Reference Values:
No established reference values


Oxalate, Plasma

Clinical Information: Oxalate is an insoluble dicarboxylic acid, which is an end product of liver metabolism of glyoxylate and glycerate. Humans lack an enzyme to degrade oxalate, and thus it must be eliminated by the kidney. Oxalate is a strong anion and tends to precipitate with calcium, especially in the urinary tract. Consequently, about 75% of all kidney stones contain calcium oxalate in some proportion. In renal failure oxalate is retained in the body and it can precipitate in tissues causing tissue toxicity, a condition called oxalosis. In the absence of disease, up to 90% of the body pool of oxalate is produced by hepatic metabolism and the other 10% is provided by oxalate contained in various foods. However, in the presence of gastrointestinal diseases that cause fat malabsorption the percentage absorbed from food can be much greater. The oxalate content of fruits and vegetables is quite variable, some being quite high and
others virtually zero. Oxalate is freely filtered by the glomerulus. A smaller amount is also secreted in the proximal tubule. If the glomerular filtration rate (GFR) is decreased, oxalate begins to be retained in the body. However, in persons without primary hyperoxaluria (PH) or enteric hyperoxaluria (EH) plasma levels do not exceed the normal range until the GFR decreases below 10-20 mL/min/1.73 m(2). Plasma oxalate concentration is a reflection of the body pool size. When the pool increases, oxalate may precipitate in tissues and cause toxicity. Plasma oxalate pool size can be increased in various situations: Increased production and accumulation results from an abnormality in at least 3 different enzymes:

Alanine glyoxalate transferase is necessary for the conversion of glycolate to alanine. A deficiency or intracellular mistargeting of this hepatic enzyme results in increased oxalate production (primary hyperoxaluria type 1). Glycolate reductase / hydroxypyruvate reductase deficiency in the liver and elsewhere in the body results in increased glyceral acid formation, which leads to increased oxalate production (primary hyperoxaluria type 2). A third type of PH was recently shown to be due to mutations of HOGA1 that encodes the enzyme 4-hydroxy-2-oxalocarboxylate aldolase that is found in hepatic mitochondria (primary hyperoxaluria type 3). Increased oxalate load can be caused by increased absorption from the intestines after consuming large amounts of oxalate-rich foods such as rhubarb, spinach, or nuts. Certain abnormalities of the gastrointestinal tract can cause fat malabsorption including short bowel syndromes, inflammatory bowel disease, gastric bypass for obesity, and pancreatic insufficiency. All of these gastrointestinal abnormalities result in increased oxalate absorption from the intestinal tract. This is due to saponification of calcium by fatty acids in the colon, which in turn frees up oxalate anions for absorption. Decreased urinary oxalate excretion in chronic kidney disease (CKD) also caused oxalate retention in the body. Management of patients with PH and renal failure is difficult. Intensive dialyses are undertaken in an attempt to keep plasma levels below the level at which supersaturation and crystallization can occur in body tissues such as heart and bones (called oxalosis). PH is typically diagnosed by measuring oxalate levels in urine. However, as kidney function decreases, the renal excretion of oxalate also decreases. In such situations, plasma oxalate levels may be informative. Although plasma oxalate increases in CKD patients without PH, values are much higher in those CKD patients who do have PH. Plasma oxalate is often used to monitor these patients during critical periods in and around kidney transplantation, dialysis, or liver transplantation. Oxalate concentration in dialysate fluid is a reflection of the oxalate removed during dialysis.

**Useful For:** Assessing the body pool size of oxalate. The settings in which it has been most useful include patients with enzyme deficiencies, such as primary hyperoxaluria, which result in overproduction of oxalate or patients with enteric hyperoxaluria (EH). In the presence of chronic kidney disease (CKD), 3 uses of plasma oxalate are: -If primary hyperoxaluria (PH) is suspected in a patient with CKD of indeterminate cause, and urinary oxalate is not available, plasma oxalate can be used to aid in diagnosis. However although plasma oxalate levels are markedly elevated in PH patients with CKD suggesting the diagnosis, ancillary tests often are necessary to confirm it, such as genetic analysis of the 3 causative genes, or pathologic demonstration of oxalate crystals in tissues -Monitoring patients with renal failure and primary or enteric hyperoxaluria in order to be sure they are receiving enough dialysis -An aid in maintaining plasma oxalate levels below supersaturation (25-30 mcmol/L)

**Interpretation:** In nonacidified plasma specimens values near the reference range increase an average of 50% due to spontaneous oxalate generation. In patients with normal renal function, the presence of increased plasma oxalate concentration is good evidence for overproduction of oxalate (primary hyperoxaluria). In the presence of renal insufficiency, plasma oxalate levels are markedly elevated. Increased levels of plasma oxalate can be found in dialysis patients. In patients with possible primary hyperoxaluria and renal insufficiency, the diagnosis often can be made by knowing the plasma level of oxalate. However, ancillary tests, such as the demonstration of oxalate crystals in tissues (other than the kidney) or increased glycolate in dialysate (for patients on dialysis) often are necessary to make an accurate diagnosis.

**Reference Values:**

<1.6 mcmol/L

Reference values have not been established for patients under 21 and greater than 81 years of age.

**Clinical References:**

**FOXAZ 90108**

**Oxazepam (Serax), Serum**

**Reference Values:**
Reference Range: 200 - 500 ng/mL

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**OMHC 81030**

**Oxcarbazepine Metabolite (MHC), Serum**

**Clinical Information:** Oxcarbazepine (OCBZ) is approved as monotherapy and adjunctive therapy for partial seizures with and without secondary generalized seizures in adults and as adjunctive therapy for partial seizures in children. In humans, OCBZ is a prodrug that is almost immediately and completely metabolized to 10-hydroxy-10,11-dihydrocarbamazepine, known as monohydroxycarbamazepine (MHC), an active metabolite that is responsible for OCBZ's therapeutic effect. The elimination half-life is 1 to 2.5 hours for OCBZ and 8 to 10 hours for MHC. The therapeutic range (3â€“35 mcg/mL) is based on concentrations of the metabolite, not the parent drug; this assay measures the metabolite only. In clinical practice, the OCBZ dosage should be individually adjusted for each patient to achieve the desired therapeutic response. Toxicity associated with OCBZ includes hyponatremia, dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait. These toxicities may be observed when blood concentrations are in the therapeutic range.

**Useful For:** Monitoring serum concentration during oxcarbazepine therapy Assessing compliance Assessing potential toxicity

**Interpretation:** Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Most individuals display optimal response to oxcarbazepine therapy when serum levels of the metabolite (measured in this assay) are between 3 and 35 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range. Thus, interpretation should include clinical evaluation.

**Reference Values:**
Oxcarbazepine metabolite: 3-35 mcg/mL

**Clinical References:**

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**FOFUS 75112**

**Oxycodone - Free (Unconjugated), Serum**

**Reference Values:**
Reporting Limit determined each analysis.

Oxycodone â€“ Free

Synonym(s): Roxicodone; OxyContin

Adult therapeutic range: 13 â€“ 120 ng/mL

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**OXYSX 61727**

**Oxycodone Screen, Chain of Custody, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone). Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure
to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detection of oxycodone and oxymorphone in urine following chain-of-custody procedures. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (e.g., OXYCU / Oxycodone with Metabolite Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/print-on-demand-select.php

**Reference Values:**

Negative

Screening cutoff concentration:

Oxycodone: 100 ng/mL

**Clinical References:**

3. Cone EJ: Oxycodone Involvement in Drug Abuse Deaths: A DAWN-Based Classification Scheme applied to an Oxycodone Postmortem Database Containing over 1000 Cases. J Anal Toxicol 2003;27:57-67

**Oxycodone Screen, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (e.g., codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone). Oxycodone is metabolized to noroxycodone, oxymorphone and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone.

**Useful For:** Detection of oxycodone and oxymorphone in urine

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (e.g., OXYCU / Oxycodone with Metabolite Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html

**Reference Values:**

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Screening cutoff concentration:

Oxycodone: 100 ng/mL

**Clinical References:**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (e.g., codeine, hydrocodone, hydromorphone, oxycodone). Oxycodone is metabolized to noroxycodone, oxymorphone and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and quantification of oxycodone and oxymorphone in urine. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

- **Negative**
  - Cutoff concentrations:
    - Oxycodone Immunoassay screen: <100 ng/mL
    - Oxycodone: 100 ng/mL
    - Oxymorphone: 100 ng/mL

**Clinical References:**

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative
- Cutoff concentrations:
  - Oxycodone: 100 ng/mL
  - Oxymorphone: 100 ng/mL

**Clinical References:**

**P50P 37950**

**Oxygen Dissociation P50**

**Reference Values:**
- > or =12 months: 24-30 mm Hg
- Reference values have not been established for patients who are <12 months of age.

**P50B 81432**

**Oxygen Dissociation, P50, Erythrocytes**

**Clinical Information:** Abnormal oxygen affinity is demonstrated in the presence of some hemoglobin variants: -High oxygen affinity causes erythrocytosis -Low oxygen affinity causes cyanosis and/or low oxygen saturation. Increased oxygen affinity of hemoglobin, reflected in a low p50, left-shifted oxygen dissociation curve, and loss of normal sigmoidal configuration, are characteristic of many hemoglobin variants that are responsible for polycythemia. Measurement of oxygen affinity is an important method for diagnosis of these disorders.

**Useful For:** Identifying hemoglobin variants associated with polycythemia or cyanotic and hypoxic disorders

**Interpretation:** Normal: p50 =24 to 30 mm Hg (with sigmoidal oxygen dissociation curve)

**Reference Values:**
- > or =12 months: 24-30 mm Hg
- Reference values have not been established for patients who are <12 months of age.


**OXYMU 62622**

**Oxymorphone Confirmation, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone). Oxycodone is metabolized to noroxycodone, oxymorphone and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone.

**Useful For:** Detection and quantification of oxymorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the
unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative
- Cutoff concentrations:
  - Oxymorphone: 100 ng/mL

**Clinical References:**

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**Oxysterols, Blood Spots**

**Clinical Information:** Niemann-Pick disease types A, B, and C are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick types A and B (NPA and NPB, OMIM 257200 and 607616) are caused by a deficiency of sphingomyelinase resulting in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of NPA or NPB is based on the age of onset as well as the severity of symptoms. NPA disease is more severe and characterized by early onset with feeding problems, dystrophy, persistent jaundice, cherry red maculae, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness. Individuals with NPA typically die by age 3. NPB disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by mutations in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are pan-ethnic. Individuals with NPD types A and B typically have elevation of the oxysterol lyso-sphingomyelin (LSM); cholestane-3 beta, 5 alpha, 6 beta-triol (COT), and/or 7-ketocholesterol (7-KC) may also be elevated. Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis). Niemann-Pick disease type C (NPC, OMIM 257220) is caused by a defect in cellular cholesterol trafficking that results in the accumulation of unesterified cholesterol in late endosomes/lysosomes. Age of onset is variable and ranges from the perinatal period to adulthood, and clinical presentation is also highly variable. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000-150,000 live births. NPC is an autosomal recessive condition and is caused by mutations in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol cholestane-3 beta, 5 alpha, 6 beta-triol (COT); 7-ketocholesterol (7-KC) may also be elevated. For molecular confirmation, genetic testing for NPC disease can be performed (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis).

**Useful For:** Investigation of possible diagnoses of Niemann-Pick disease type C (NPC) and types A or B (NPA or NPB) Monitoring of individuals with NPC disease

**Interpretation:** An elevation of cholestane-3 beta, 5 alpha, 6 beta-triol (COT) is highly suggestive of Niemann-Pick disease type C disease. An elevation of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick disease type A or B disease.

**Reference Values:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestane-3beta, 5alpha, 6beta-triol</td>
<td>&lt; or =0.62 nmol/mL</td>
</tr>
<tr>
<td>Lyso-sphingomyelin</td>
<td>&lt; or =0.20 nmol/mL</td>
</tr>
</tbody>
</table>

Oxysterols, Plasma

Clinical Information: Niemann-Pick disease types A, B, and C are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick types A and B (NPA and NPB), are caused by a deficiency of sphingomyelinase resulting in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of NPA or NPB is based on age of onset as well as the severity of symptoms. NPA disease is more severe and characterized by early onset with feeding problems, dystrophy, persistent jaundice, cherry red maculae, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness. Individuals with NPA typically die by age 3. NPB disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by mutations in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are pan-ethnic. Individuals with NPD types A and B typically have elevation of the oxysterol lyso-sphingomyelin (LSM); cholestane-3,5,6-triol (COT) and/or 7-ketocholesterol (7-KC) may also be elevated. Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis). Niemann-Pick disease type C (NPC, OMIM 257220) is caused by a defect in cellular cholesterol trafficking that results in the accumulation of unesterified cholesterol in late endosomes/lysosomes. Age of onset is variable and ranges from the perinatal period to adulthood, and clinical presentation is also highly variable. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Infants may present with or without hepatosplenomegalgy and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000-150,000 live births. NPC is an autosomal recessive condition and is caused by mutations in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol cholestane-3 beta,5 alpha,6 beta-triol (COT); 7-ketocholesterol (7-KC) may also be elevated. For molecular confirmation, genetic testing for NPC disease can be performed (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis).

Useful For: Investigation of possible diagnoses of Niemann-Pick disease type C (NPC) and types A or B (NPA or NPB) Monitoring of individuals with Niemann-Pick type C disease

Interpretation: An elevation of cholestane-3 beta,5 alpha,6 beta-triol (COT) is highly suggestive of NPC disease. An elevation of lyso-sphingomyelin (LSM) is highly suggestive of NP type A or B disease.

Reference Values:
CHOLESTANE-3BETA, 5ALPHA, 5BETA-TRIOL
Cutoff: < or =0.02 nmol/mL

7-KETOCHOLESTEROL
Cutoff: < or =0.05 nmol/mL

LYSO-SPHINGOMYELIN
Cutoff: < or =0.02 nmol/mL

Oyster, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
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<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

P0 (Pzero) Antibodies

**Interpretation:** Antibodies against P0 protein occur in 46% of patients with Meniere’s disease, 40% of patients with otosclerosis, 28% of patients with idiopathic progressive sensorineural hearing loss and 18% of patients with sudden deafness and in 4% of control subjects (Tomasi JP, Lona A, Deggouj N, Gersdorff M. Autoimmune sensorineural hearing loss in young patients: an exploratory study. Laryngoscope, 2001;111:2050-3v)

**Reference Values:**
Qualitative Test â€“ Positive or Negative

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Pacific Squid, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Clinical Information: This profile was designed to test for and confirm the most common classes of drugs of abuse. Opiate confirmation is performed on all specimens by liquid chromatography-tandem mass spectrometry (LC-MS/MS). This profile uses immunoassay testing for drugs of abuse by class. All positive screening results are confirmed by gas chromatography/mass spectrometry or LC-MS/MS.

Useful For: Detection and identification of drugs of abuse This test is intended to be used in a setting where the identification of the drug is required.

Interpretation: A positive result derived by this testing indicates that the patient has been exposed in the recent past to the drugs identified. Positive results are definitive. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, contact Mayo Medical Laboratories at 800-533-1710.

Reference Values:
Negative for drugs of abuse

DAU:
Enzyme-multiplied immunoassay technique screening cutoff concentration:
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 200 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Methadone: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

MSOP:
Positive cutoff concentrations
Codeine: <100 ng/mL
Hydrocodone: <100 ng/mL
Hydromorphone: <100 ng/mL
Morphine: <100 ng/mL
Oxycodone: <100 ng/mL
Oxymorphone: <100 ng/mL


Pain Clinic Drug Screen, Urine

Clinical Information: This panel was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID) the following drugs: -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This panel uses the screening technique which involves immunoassay testing for drugs by class. All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS, and quantitated, before a positive result is reported. The panel includes PSDU / Drug Screen, Prescription/OTC, Urine, which looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians
manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be
due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The
test is not designed to screen for intermittent use of illicit drugs.

**Useful For:** Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine,
ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol. Detection and identification of
prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent.
This test is intended to be used in a setting where the identification of the drug is required.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent
past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For
information about drug testing, including estimated detection times, see Drugs of Abuse Testing at

**Reference Values:**

- **Negative**
  - Screening cutoff concentrations:
    - Amphetamines: 500 ng/mL
    - Barbiturates: 200 ng/mL
    - Benzodiazepines: 100 ng/mL
    - Cocaine (benzoylcgonine-cocaine metabolite): 150 ng/mL
    - Ethanol: 10 mg/dL
    - Methadone metabolite: 300 ng/mL
    - Opiates: 300 ng/mL
    - Phencyclidine: 25 ng/mL
    - Tetrahydrocannabinol carboxylic acid: 50 ng/mL

- This report is intended for use in clinical monitoring or management of patients. It is not intended for use
  in employment-related testing.

**Clinical References:**
Saunders Company. 2011, pp 1109-1188
Washington, DC. AACC Press, 2003, p 385

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**PN_10**

**Pain Clinic Survey 10**

**Reference Values:**
Only orderable as part of a profile. For more information see PAINO / Pain Clinic Survey 10, Urine.

**PN10X**

**Pain Clinic Survey 10, Chain of Custody**

**Reference Values:**
Only orderable as part of a profile. For more information see PANOX / Pain Clinic Survey 10, Chain of Custody, Urine.

**PANOX**

**Pain Clinic Survey 10, Chain of Custody, Urine**

**Clinical Information:** This assay was designed to test for and confirm by gas chromatography-mass
spectrometry (GC-MS) the following: -Barbiturates -Benzodiazepines -Cocaine -Methadone
-Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry
(LC-MS/MS) is completed for all opiates and amphetamines. This test uses the simple screening
technique which involves immunologic testing for drugs by class. Oxycodone is not detected well with
the opiate screening assay; therefore, OPATX / Opiate Confirmation, Chain of Custody, Urine is included
to detect this drug. All positive screening results are confirmed by GC-MS or LC-MS/MS, and
quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This chain-of-custody test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

**Interpretation:** A positive result derived by this testing indicates that the patient has used 1 of the drugs detected by this technique in the recent past. See individual tests (e.g., AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html

**Reference Values:**

**Negative**

- Screening cutoff concentrations
  - Amphetamines: 500 ng/mL
  - Barbiturates: 200 ng/mL
  - Benzodiazepines: 100 ng/mL
  - Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
  - Methadone metabolite: 300 ng/mL
  - Opiates: 300 ng/mL
  - Phencyclidine: 25 ng/mL
  - Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Clinical References:**


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**PAINO 36070**

**Pain Clinic Survey 10, Urine**

**Clinical Information:** This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) the following: -Barbiturates -Benzodiazepines -Cocaine -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS or LC-MS/MS, and quantitated, before a positive result is reported.

**Useful For:** Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

**Interpretation:** A positive result derived by this testing indicates that the patient has used 1 of the drugs detected by this technique in the recent past. See individual tests (e.g., AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/articles/drug-book/index.html

**Reference Values:**

**Negative**
Screening cutoff concentrations:
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Oxycodone: 100 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Clinical References:**

**FPANS 57129**
Pancreasstatin
Reference Values:
0-88 pg/mL

**FPANC 91415**
Pancreatic Elastase Stool
**Clinical Information:** This assay allows the diagnosis or exclusion of pancreatic exocrine insufficiency, which can be caused by chronic pancreatitis, cystic fibrosis, pancreatic tumor, cholelithiasis or diabetes mellitus.

**Reference Values:**
>200 ug Elastase/g stool = Normal
100 to 200 ug Elastase/g stool = Moderate to slight exocrine pancreatic insufficiency
<100 ug Elastase/g stool = Severe exocrine pancreatic insufficiency

**HPP 8014**
Pancreatic Polypeptide, Plasma
**Clinical Information:** Pancreatic polypeptide (PP) is secreted by the pancreas in response to hypoglycemia, ingestion of food, or "sham" feeding (food is chewed, but not swallowed), secondary to vagal nerve stimulation. Secretion is blocked by vagotomy or atropine. The exact physiologic role of PP is undetermined, although the hormone is thought to be involved in exocrine pancreatic secretion and gallbladder emptying. Markedly elevated levels are often associated with endocrine tumors of the pancreas (eg, insulinoma, glucagonoma, PPoma: pancreatic polypeptide-secreting tumor of the pancreas). Patients with diabetes may also have elevated PP levels. A lack of response to sham feeding may indicate vagal nerve damage (eg, surgery-related nerve damage, autonomic nerve disorders). Extensive pancreatic destruction (eg, chronic pancreatitis, pancreatic cancer) may also result in low basal PP levels and a lack of response to sham feeding.

**Useful For:** Detection of pancreatic endocrine tumors Assessment of vagal nerve function after meal or sham feeding

**Interpretation:** High levels may be seen in pancreatic endocrine tumors, diabetes, and a nonfasting state. Markedly elevated levels may be seen in some pancreatic exocrine tumors. A normal response to a sham feeding consists of a rapid pancreatic polypeptide (PP) rise over baseline followed by a return to baseline. With vagal damage, no increase over baseline is seen.
**Reference Values:**
- 0-19 years: not established
- 20-29 years: < 228 pg/mL
- 30-39 years: < 249 pg/mL
- 40-49 years: < 270 pg/mL
- 50-59 years: < 291 pg/mL
- 60-69 years: < 312 pg/mL
- 70-79 years: < 332 pg/mL
- > or = 80 years: not established

**Clinical References:**

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**PAPN 82383 Papain, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
**Papaya, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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</tbody>
</table>

sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**PARAV 80421**

**Parainfluenza Virus (Types 1, 2, 3) Antibodies, Serum**

**Reference Values:**

REFERENCE RANGE: < 1:8

INTERPRETIVE CRITERIA:

< 1:8 Antibody Not Detected
> or =1:8 Antibody Detected

Single titers > or = 1:64 are indicative of recent infection. Titers of 1:8 to 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. After initial infection, antibody responses at a later date are often heterotypic and exhibit crossreactivity with other paramyxoviruses (e.g., mumps).

**PAVAL 83380**

**Paraneoplastic Autoantibody Evaluation, Serum**

**Clinical Information:** Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons, glia, or muscle...
are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. Cancers recognized in this context most commonly are small-cell lung carcinoma, thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient’s autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Four classes of autoantibodies are recognized in this evaluation:

- Neuronal nuclear (ANNA-1, ANNA-2, ANNA-3) - Anti-glial/neuronal nuclear (AGNA-1; also known as Sox1)
- Neuronal and muscle cytoplasmic (PCA-1, PCA-2, PCA-Tr, CRMP-5, amphiphysin, and striational)
- Plasma membrane cation channel, calcium channels, P/Q-type and N-type calcium channel, dendrotoxin-sensitive potassium channels, and neuronal (ganglionic) and muscle nicotinic acetylcholine receptors (AChR). These autoantibodies are potential effectors of neurological dysfunction. Seropositive patients usually present with subacute neurological symptoms and signs such as encephalopathy; cerebellar ataxia; myelopathy; radiculopathy; plexopathy; or sensory, sensorimotor, or autoimmune neuropathy, with or without a neuromuscular transmission disorder: Lambert-Eaton syndrome, myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

**Useful For:** Serological evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer. Directing a focused search for cancer Investigating neurological symptoms that appear in the course of, or after, cancer therapy, and are not explainable by metastasis. Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy. Monitoring the immune response of seropositive patients in the course of cancer therapy. Detecting early evidence of cancer recurrence in previously seropositive patients.

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient’s immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1) 
  \(< 1:240\)
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2) 
  \(< 1:240\)
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3) 
  \(< 1:240\)
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) 
  \(< 1:240\)

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) 
  \(< 1:240\)
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) 
  \(< 1:240\)
- Purkinje Cell Cytoplasmic Antibody, Type Tr (PCA-Tr) 
  \(< 1:240\)
- Amphiphysin Antibody 
  \(< 1:240\)
- CRMP-5-IgG 
  \(< 1:240\)
Note: Titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 or 507-266-5700 to request CRMP-5 Western blot.

Striational (Striated Muscle) Antibodies

<1:120

CATION CHANNEL ANTIBODIES

N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, or CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

ACHR RECEPTOR ANTIBODIES

ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L
AChR Receptor (Muscle) Modulating Antibody
0-20% loss of AChR

NEUROMYELITIS OPTICA (NMO)/AQUAPORIN-4-IGG CELL-BINDING ASSAY

Negative
Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative
N-Methyl-D-aspartate receptor (NMDA-R) CBA
Negative
IFA <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R) CBA
Negative
IFA <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R) CBA
Negative
IFA <1:120

Paraneoplastic Autoantibody Evaluation, Spinal Fluid

Clinical Information: Several antineuronal and glial autoantibodies are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). Seropositive patients present with neurologic symptoms and signs in >90% of cases. The cancers are most commonly small-cell lung carcinoma, ovarian (or related mullerian) carcinoma, breast carcinoma, thymoma, or Hodgkin lymphoma. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures. Detection of the informative marker autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve survival. Serum is the preferred specimen for paraneoplastic autoantibodies. However, cerebrospinal fluid (CSF) results are sometimes positive when serum results are negative (especially for CRMP-5 and other inflammatory central nervous system autoimmunity). Additionally, CSF is more readily interpretable because it generally lacks the interfering nonorgan-specific antibodies that are common in serum of patients with cancer. Because neurologists typically perform spinal taps in these patients, we recommend that CSF be submitted with serum, either for simultaneous testing or to be held for testing only if serum is negative. CRMP-5-IgG Western blot is also performed by specific request for more sensitive detection of CRMP-5-IgG. Testing should be requested in cases of subacute basal ganglionic disorders (chorea, Parkinsonism), cranial neuropathies (especially loss of vision, taste, or smell), and myelopathies.

Useful For: Aids in the diagnosis of paraneoplastic neurological autoimmune disorders related to carcinoma of lung, breast, ovary, thymoma, or Hodgkin lymphoma

Interpretation: Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer. In patients with a history of tobacco use or other lung cancer risk, or if thymoma is suspected, PAVAL / Paraneoplastic Autoantibody Evaluation, Serum is also recommended.

Reference Values:
NEURONAL NUCLEAR ANTIBODIES
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1) Negative at <1:2
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2) Negative at <1:2
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3) Negative at <1:2
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) Negative at <1:2

NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) Negative at <1:2
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) Negative at <1:2
- Purkinje Cell Cytoplasmic Antibody, Type TR (PCA-TR) Negative at <1:2
- Amphiphysin Antibody Negative at <1:2
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IGG) Negative at <1:2
ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody Assay
< or =0.02 nmol/L

WESTERN BLOT
Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative

N-Methyl-D-aspartate receptor (NMDA-R)
CBA: Negative
IFA <1:2
2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid receptor (AMPA-R)
CBA: Negative
IFA <1:2
Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
CBA: Negative
IFA <1:2
NMO/AQP4-IgG
Negative
VGKC-Complex Antibody IPA
< or=0.02 nmol/L

Clinical References:

PARID 9202
Parasite Identification

Clinical Information: Infectious diseases are spread and caused by a variety of macroscopic vectors. A wide array of macroscopic parasites (worms and ectoparasites) and parasite mimics or artifacts may be submitted for examination and identification. It is important to promptly and accurately identify these specimens so that the ordering physician can appropriately treat and counsel the patient.

Useful For: Gross identification of parasites (eg, worms) and arthropods (eg, ticks, bed bugs, lice, mites) Detecting or eliminating the suspicion of parasitic infection by identifying suspect material passed in stool or found on the body Diagnosing delusional parasitosis Identifying ticks, including Ixodes (carrier of Lyme disease)

Interpretation: A descriptive report is provided identifying the worm or arthropod. Worms and hard ticks are identified to the species level when possible, while other parasitic arthropods are identified to the genus level. Arthropods that do not cause human disease and parasite mimics resembling worms are
Parasitic Examination

Clinical Information: A variety of different parasites may be found in stool specimens, duodenal aspirates, respiratory specimens, liver cyst aspirates/abscesses and tissues. These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (aka worms). Infection is often asymptomatic, but symptoms range from diarrhea and malnutrition, intestinal obstruction, and rarely, death. The most common intestinal reported parasites in stool specimens are Giardia intestinalis (aka Giardia duodenalis, Giardia lamblia) and Cryptosporidium species. Both parasites may cause watery diarrhea and are endemic in the United States. The best tests for these 2 common parasites are parasite-specific fecal antigen tests (GIAR / Giardia Antigen, Feces and CRYPS / Cryptosporidium Antigen, Feces). Other parasites are less commonly seen in the United States, and the stool parasitic exam is the appropriate test for their detection. See Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for determining which test should be ordered based on the patient’s exposure history and risk factors.

Useful For: Detection and identification of parasitic protozoa and the eggs and larvae of parasitic helminths

Interpretation: A positive result indicates the presence of the parasite but does not necessarily indicate that it is the cause of any symptoms. Some strains of protozoa are nonpathogenic and some helminths cause little or no illness.

Reference Values:
Negative
If positive, organism identified


Parathyroid Hormone (PTH), Serum

Clinical Information: Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. The hormone is synthesized as a 115-amino acid precursor (pre-pro-PTH), cleaved to pro-PTH and then to the 84-amino acid molecule, PTH (numbering, by universal convention, starting at the amino-terminus). The precursor forms generally remain within the parathyroid cells. Secreted PTH undergoes cleavage and metabolism to form carboxyl-terminal fragments (PTH-C), amino-terminal fragments (PTH-N), and mid-molecule fragments (PTH-M). Only those portions of the molecule that carry the amino terminus (ie, the whole molecule and PTH-N) are biologically active. The active forms have half-lives of approximately 5 minutes. The inactive PTH-C fragments, with half-lives of 24 to 36 hours, make up >90% of the total circulating PTH and are primarily cleared by the kidneys. In patients with renal failure, PTH-C fragments can accumulate to high levels. PTH 1-84 is also elevated in these patients, with mild elevations being considered a beneficial compensatory response to end organ PTH resistance, which is observed in renal failure. The serum calcium level regulates PTH secretion via negative feedback through the parathyroid calcium sensing receptor (CASR). Decreased calcium levels stimulate PTH release. Secreted PTH interacts with its specific type II G-protein receptor, causing rapid increases in renal tubular reabsorption of calcium and decreased phosphorus reabsorption. It also participates in long-term calciostatic functions by enhancing mobilization of calcium from bone and increasing renal synthesis of 1,25-dihydroxy vitamin D, which, in
turn, increases intestinal calcium absorption. In rare inherited syndromes of parathyroid hormone resistance or unresponsiveness and in renal failure, PTH release may not increase serum calcium levels. Hyperparathyroidism causes hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. Long-term consequences are dehydration, renal stones, hypertension, gastrointestinal disturbances, osteoporosis and sometimes neuropsychiatric and neuromuscular problems. Hyperparathyroidism is most commonly primary and caused by parathyroid adenomas. It can also be secondary in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in renal failure. Long-standing secondary hyperparathyroidism can result in tertiary hyperparathyroidism, which represents the secondary development of autonomous parathyroid hypersecretion. Rare cases of mild, benign hyperparathyroidism can be caused by inactivating CASR mutations. Hypoparathyroidism is most commonly secondary to thyroid surgery, but can also occur on an autoimmune basis, or due to activating CASR mutations. The symptoms of hypoparathyroidism are primarily those of hypocalcemia, with weakness, tetany, and possible optic nerve atrophy.

**Useful For:** Diagnosis and differential diagnosis of hypercalcemia Diagnosis of primary, secondary, and tertiary hyperparathyroidism Diagnosis of hypoparathyroidism Monitoring end-stage renal failure patients for possible renal osteodystrophy

**Interpretation:** About 90% of the patients with primary hyperparathyroidism have elevated parathyroid hormone (PTH) levels. The remaining patients have normal (inappropriate for the elevated calcium level) PTH levels. About 40% of the patients with primary hyperparathyroidism have serum phosphorus levels <2.5 mg/dL and about 80% have serum phosphorus <3.0 mg/dL. An (appropriately) low PTH level and high phosphorus level in a hypercalcemic patient suggests that the hypercalcemia is not caused by PTH or PTH-like substances. An (appropriately) low PTH level with a low phosphorus level in a hypercalcemic patient suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid related peptide (PTHRP). PTHRP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types. A low or normal PTH in a patient with hypocalcemia suggests hypoparathyroidism, provided the serum magnesium level is normal. Low magnesium levels inhibit PTH release and action and can mimic hypoparathyroidism. Low serum calcium and high PTH levels in a patient with normal renal function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bio-ineffective PTH. A limited number of the PTH-C fragments, which accumulate in renal failure, chiefly PTH 7-84, cross-react in this and other intact PTH assays. PTH 1-84 is also elevated in renal failure, with mild elevations being considered beneficial. Consequently, when measured with an intact PTH assay, concentrations of 1.5 to 3 times the upper limit of the healthy reference range appear to represent the optimal range for end-stage renal failure patients. Lower concentrations may be associated with adynamic renal bone disease, while higher levels suggest possible secondary or tertiary hyperparathyroidism, which can result in high-turnover renal osteodystrophy. Some patients with moderate hypercalcemia and equivocal phosphate levels, who have either mild elevations in PTH or (inappropriately) normal PTH levels, may be suffering from familial hypocalciuric hypercalcemia, which is due to inactivating CASR mutations. The molar renal calcium to creatinine clearance is typically <0.01 in these individuals. The condition can be confirmed by CASR gene mutation screening (CSRSP / Calcium Sensing Receptor [CASR] Gene, Full Gene Analysis).

**Reference Values:**
15-65 pg/mL
Reference values apply to all ages.

**Clinical References:**
Parathyroid Hormone (PTH), with Minerals, Serum

Clinical Information: Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. The hormone is synthesized as a 115-amino acid precursor (pre-pro-PTH), cleaved to pro-PTH and then to the 84-amino acid molecule, PTH (numbering, by universal convention, starting at the amino-terminus). The precursor forms generally remain within the parathyroid cells. Secreted PTH undergoes cleavage and metabolism to form carboxyl-terminal fragments (PTH-C), amino-terminal fragments (PTH-N), and mid-molecule fragments (PTH-M). Only those portions of the molecule that carry the amino terminus (ie, the whole molecule and PTH-N) are biologically active. The active forms have half-lives of approximately 5 minutes. The inactive PTH-C fragments, with half-lives of 24 to 36 hours, make up >90% of the total circulating PTH and are primarily cleared by the kidneys. In patients with renal failure, PTH-C fragments can accumulate to high levels. PTH 1-84 is also elevated in these patients, with mild elevations being considered a beneficial compensatory response to end organ PTH resistance, which is observed in renal failure. The serum calcium level regulates PTH secretion via negative feedback through the parathyroid calcium sensing receptor (CASR). Decreased calcium levels stimulate PTH release. Secreted PTH interacts with its specific type II G-protein receptor, causing rapid increases in renal tubular reabsorption of calcium and decreased phosphorus reabsorption. It also participates in long-term calciostatic functions by enhancing mobilization of calcium from bone and increasing renal synthesis of 1,25-dihydroxy vitamin D, which, in turn, increases intestinal calcium absorption. In rare inherited syndromes of parathyroid hormone resistance or unresponsiveness and in renal failure, PTH release may not increase serum calcium levels. Hyperparathyroidism causes hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. Long-term consequences are dehydration, renal stones, hypertension, gastrointestinal disturbances, osteoporosis, and sometimes neuropsychiatric and neuromuscular problems. Hyperparathyroidism is most commonly primary and caused by parathyroid adenomas. It can also be secondary in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in renal failure. Long-standing secondary hyperparathyroidism can result in tertiary hyperparathyroidism, which represents the secondary development of autonomous parathyroid hypersecretion. Rare cases of mild, benign hyperparathyroidism can be caused by inactivating CASR mutations. Hypoparathyroidism is most commonly secondary to thyroid surgery, but can also occur on an autoimmune basis, or due to activating CASR mutations. The symptoms of hypoparathyroidism are primarily those of hypocalcemia, with weakness, tetany, and possible optic nerve atrophy.

Useful For: Diagnosis and differential diagnosis of hypercalcemia Diagnosis of primary, secondary, and tertiary hyperparathyroidism Diagnosis of hypoparathyroidism Monitoring endstage renal failure patients for possible renal osteodystrophy

Interpretation: About 90% of the patients with primary hyperparathyroidism have elevated parathyroid hormone (PTH) levels. The remaining patients have normal (inappropriate for the elevated calcium level) PTH levels. About 40% of the patients with primary hyperparathyroidism have serum phosphorus levels <2.5 mg/dL and about 80% have serum phosphorus <3.0 mg/dL. An (appropriately) low PTH level and high phosphorus level in a hypercalcemic patient suggests that the hypercalcemia is not caused by PTH or PTH-like substances. An (appropriately) low PTH level with a low phosphorus level in a hypercalcemic patient suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid-related peptide (PTHRP). PTHRP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types. A low or normal PTH in a patient with hypocalcemia suggests hypoparathyroidism, provided the serum magnesium level is normal. Low magnesium levels inhibit PTH release and action and can mimic hypoparathyroidism. Low serum calcium and high PTH levels in a patient with normal renal function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bioineffective PTH. A limited number of the PTH-C fragments, which accumulate in renal failure, chiefly PTH 7-84, cross-react in this and other intact PTH assays. PTH 1-84 is also elevated in renal failure, with mild elevations being considered beneficial. Consequently, when measured with an intact PTH assay, concentrations of 1.5 to 3 times the upper limit of the healthy reference range appear to represent the optimal range for end-stage renal failure patients. Lower concentrations may be associated with adynamic renal bone disease, while
Higher levels suggest possible secondary or tertiary hyperparathyroidism, which can result in high-turnover renal osteodystrophy. Some patients with moderate hypercalcemia and equivocal phosphate levels, who have either mild elevations in PTH or (inappropriately) normal PTH levels, may be suffering from familial hypocalciuric hypercalcemia, which is due to inactivating CASR mutations. The molar renal calcium to creatinine clearance is typically <0.01 in these individuals. The condition can be confirmed by CASR gene mutation screening (CSRSP / Calcium Sensing Receptor [CASR] Gene, Full Gene Analysis).

Reference Values:

**PARATHYROID HORMONE**

15-65 pg/mL

Reference values apply to all ages.

**CALCIUM**

Males

0-11 months: not established*
1-14 years: 9.6-10.6 mg/dL
15-16 years: 9.5-10.5 mg/dL
17-18 years: 9.5-10.4 mg/dL
19-21 years: 9.3-10.3 mg/dL
> or =22 years: 8.9-10.1 mg/dL

Females

0-11 months: not established*
1-11 years: 9.6-10.6 mg/dL
12-14 years: 9.5-10.4 mg/dL
15-18 years: 9.1-10.3 mg/dL
> or =19 years: 8.9-10.1 mg/dL

**PHOSPHORUS**

Males

0-11 months: not established**
1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL

Females

0-11 months: not established**
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL

**CREATININE**

Males

0-11 months: not established
1-2 years: 0.1-0.4 mg/dL
3-4 years: 0.1-0.5 mg/dL
5-9 years: 0.2-0.6 mg/dL
10-11 years: 0.3-0.7 mg/dL
12-13 years: 0.4-0.8 mg/dL
14-15 years: 0.5-0.9 mg/dL
> or =16 years: 0.8-1.3 mg/dL

Females

0-11 months: not established
1-3 years: 0.1-0.4 mg/dL
4-5 years: 0.2-0.5 mg/dL
6-8 years: 0.3-0.6 mg/dL
9-15 years: 0.4-0.7 mg/dL
> or =16 years: 0.6-1.1 mg/dL.

*The serum concentration of calcium varies significantly during the immediate neonatal period. In general, the serum calcium concentration decreases over the first days of life, followed by a gradual increase to adult concentrations by the second or third week of life.

**The plasma concentrations of inorganic phosphate in the neonatal period can be greater than those of the adult.


**Parathyroid Hormone, Fine-Needle Aspiration Biopsy (FNAB)-Needle Wash

**Clinical Information:** Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. PTH analysis in rinse material obtained from fine-needle aspiration biopsies (FNAB) has gained popularity to discriminate thyroid tissues from enlarged parathyroid glands and also to facilitate parathyroid localization prior to surgery. Various groups have reported on the utility of this technique with specificity of 91% to 100% and sensitivity of 91% to 100%. Measuring PTH in the rinse material proved very useful in cases of nondiagnostic cytology. Comparing the results of the PTH rinse material with serum PTH is highly recommended. An elevated PTH in the serum could falsely elevate PTH in the washings if the rinse is contaminated with blood. In these cases, only PTH values significantly higher than the serum should be considered as true positives. Cytologic examination and measurement of PTH can be performed on the same specimen. To measure PTH, the fine-needle aspirate (FNA) needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination has been expelled from the needle for a smear or CytoTrap preparation. Specimen collection is critical for the performance of the assay and the needle should be rinsed with a minimal volume. Each FNA needle from a single biopsied area is washed with 0.1 to 0.5 mL of normal saline. The washes from a single area are pooled (final volume 1-1.5 mL). PTH levels are measured in the saline wash.

**Useful For:** An adjunct to cytology examination of fine-needle aspiration specimens to confirm or exclude presence of parathyroid tissue in the biopsied area

**Interpretation:** Parathyroid hormone (PTH) values <100 pg/mL suggest the biopsied site does not contain PTH-secreting tissue. PTH values > or =100 pg/mL are suggestive of the presence of PTH-secreting tissue at the site biopsied or along the needle track.

**Reference Values:**
An interpretive report will be provided.

**Parathyroid Hormone-Related Peptide (PTHrP), Plasma**

**Clinical Information:** Hypercalcemia of malignancy is a common cause of hypercalcemia in hospitalized patients. Hypercalcemia of malignancy is typically not due to excess parathyroid hormone (PTH). In these disorders, PTH is usually suppressed due to elevated serum calcium concentrations. A variety of other mechanisms lead to inappropriate hypercalcemia in hypercalcemia of malignancy. These include: - Impaired renal function due to a tumor or its treatment - Osteolytic activity within bony metastases - Release of calcemic cytokines by non-osteolytic bony metastases - Ectopic 1-alpha hydroxylase activity in tumor tissues - Secretion of humoral factors mimicking PTH action (humoral hypercalcemia of malignancy: HHM), usually associated with secretion of parathyroid hormone-related peptide (PTHrP) by the primary tumor (or more commonly its metastases) - Other, as yet unknown factors

Frequently, a single cause cannot be pinpointed. Among the defined causes of the condition, PTHrP secretion is believed to be the most common culprit. PTHrP is a single monomeric peptide that exists in several isoforms, ranging from approximately 60 amino acids to 173 amino acids in size, which are created by differential splicing and post-translational processing by prohormone convertases. PTHrP is produced in low concentrations by virtually all tissues. The physiological role of PTHrP remains incompletely understood. Its functions can be broadly divided into 4 categories, not all of which are present in all PTHrP isoforms or in all tissues: - Transepithelial calcium transport, particularly in the kidney and mammary gland - Smooth muscle relaxation in the uterus, bladder, gastrointestinal tract, and arterial wall - Regulation of cellular proliferation - Cellular differentiation and apoptosis of multiple tissues - As an indispensable component of successful pregnancy and fetal development (embryonic gene deletion is lethal in mammals) PTHrP's diverse functions are mediated through a range of different receptors, which are activated by different portions of PTHrP. Among the many receptors that respond to PTHrP is the PTH receptor, courtesy of the fact that 8 of the 13 N-terminal amino acids of PTH and of 3 common PTHrP isoforms are identical. Since most of PTHrP's actions in normal physiology are autocrine or paracrine, with circulating levels being very low, this receptor cross-talk only becomes relevant when there is extreme and sustained over-production of PTHrP. This is seen occasionally in pregnancy, lactation and, rarely, in a variety of non-malignant diseases. However, most commonly it is observed when tumors secrete PTHrP ectopically. In rough correlation with physiological production levels of PTHrP in the corresponding healthy tissues, ectopic PTHrP production is most commonly seen in carcinomas of breast, lung (squamous), head and neck (squamous), kidney, bladder, cervix, uterus, and ovary. Neuroendocrine tumors may also occasionally produce PTHrP. Most other carcinomas, sarcomas, and hematolymphatic malignancies only sporadically produce PTHrP, with the notable exceptions of T-cell lymphomas and myeloma. Patients with HHM may have increased PTHrP values before treatment. PTHrP level decreases and PTH level increases, accompanied by decreased serum calcium values, with successful treatment. See Diagnostic Use of Parathyroid Hormone Assays in Publications.

**Useful For:** Diagnostic work-up of patients with suspected hypercalcemia of malignancy

**Interpretation:** Depending on the patient population, up to 80% of patients with malignant tumors and hypercalcemia will be suffering from humoral hypercalcemia of malignancy (HHM). Of these, 50% to 70% might have an elevated parathyroid hormone-related peptide (PTHrP) level. These patients will also usually show typical biochemical changes of excess parathyroid hormone (PTH)-receptor activation, namely, besides the hypercalcemia, the might have hypophosphatemia, hypercalcuria, hyperphosphaturia and elevated serum alkaline phosphatase. Their PTH levels will typically be less than 30 pg/mL or undetectable. In patients with biochemical findings that suggest but do not prove primary hyperparathyroidism (eg, hypercalcemia, but normal or near normal serum phosphate and a PTH level that is within the population reference range, but above 30 pg/mL), HHM should be considered as a diagnostic possibility, particularly if the patient is elderly, has a history of malignancy or risk factors for malignancy. An elevated PTHrP level in such a patient is highly suggestive of HHM as the cause for the hypercalcemia.

Reference Values:
<2.0 pmol/L


PPAP 52964

Parental Sample Prep for Prenatal Microarray Testing

Clinical Information: In order to interpret equivocal array results on a prenatal sample (amniotic fluid or chorionic villus), parental studies are performed to determine if the abnormality detected on the prenatal array is inherited or de novo. Maternal cell contamination testing is performed on the maternal blood and prenatal sample to detect the presence of maternal cells in the fetal sample.

Useful For: Preparing parental blood samples for possible confirmation testing if an abnormality is detected on the prenatal array sample DNA extraction of the maternal blood sample used for maternal cell contamination testing

Interpretation: No interpretation will be provided. This test is for sample processing only.

Reference Values: An interpretive report will be provided.

PCAB 83728

Parietal Cell Antibodies, IgG, Serum

Clinical Information: Pernicious anemia (PA) is characterized by atrophic body gastritis (ABG) and is the end state of a progressive disease known as autoimmune chronic atrophic gastritis.(1) In this disease, immune-mediated inflammation leads to destruction of gastric parietal cells with the resultant loss of intrinsic factor production and the inability to absorb dietary vitamin B12. Diagnosis of PA involves demonstrating the presence of a macrocytic anemia in the context of vitamin B12 deficiency, as well as documenting positive autoantibody serology, specifically anti-parietal cell antibody (PCA) and intrinsic factor antibody (IFA).(2) PCAs bind to the alpha- and beta-subunits of the membrane-bound H(+)/K(+)ATPase. In contrast, IFAs bind directly to intrinsic factor, blocking its ability to bind vitamin B12.(1,2) Both PCAs and IFAs are useful diagnostic markers for PA. In a recently published study, PCAs were 81% sensitive and 90% specific for ABG, while IFAs were 27% sensitive and 100% specific. The study concluded that a combination of PCA and IFA testing was the optimal strategy for the evaluation of patients with suspected PA.(4)

Useful For: Evaluating patients suspected of having pernicious anemia or immune-mediated deficiency of vitamin B12 with or without megaloblastic anemia

Interpretation: A positive result indicates the presence of IgG antibodies to H(+)/K(+) ATPase and suggests the possibility of pernicious anemia (PA) or a related autoimmune disease. A negative result indicates no detectable IgG antibodies to H(+)/K(+) ATPase; it does not rule out PA. An equivocal result is indeterminate.

Reference Values:
Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units
Reference values apply to all ages.


**Parietaria judaica, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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Reference values apply to all ages.


**Parietaria officinalis, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are...
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Paroxetine, Serum**

**Clinical Information:** Paroxetine (Paxil and Paxil CR) is approved for treatment of depression. Paroxetine is completely absorbed. Metabolites of paroxetine are inactive. Paroxetine metabolism is carried out by cytochrome P450 (CYP) 2D6. Paroxetine can saturate CYP2D6 resulting in a nonlinear relationship between dose and serum concentration. Paroxetine clearance is significantly affected by reduced hepatic function, but only slightly by reduced renal function. A typical adult paroxetine dose is 30 mg per day. Paroxetine is 100% bioavailable, 95% protein bound, and the apparent volume of distribution is 17 L/Kg. Time to peak serum concentration is 5 hours for the regular product and 8 hours for the controlled release product. The elimination half-life is 20 hours. Half-life is prolonged in the elderly and with cirrhosis.

**Useful For:** Monitoring paroxetine therapy Identifying noncompliance, although regular blood level monitoring is not indicated in most patients Identifying states of altered drug metabolism when used in conjunction with CYP2D6 genotyping

**Interpretation:** Steady-state serum concentrations associated with optimal response to paroxetine are
in the range of 30 to 120 ng/mL. The most common toxicities associated with excessive serum concentration are asthenia, anticholinergic effects, anxiety, blurred vision, and changes in sexual function. Toxic range: > or =400 ng/mL.

Reference Values:
30-120 ng/mL


FPRTF 57967 Parrot Australian (Budgerigar) Feathers IgE
Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive
Reference Values:
<0.35 kU/L

FPARG 57686 Parsley IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200
Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PSLY 82765 Parsley, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**Parvovirus B19 Antibodies, IgG and IgM, Serum**

**Clinical Information:** Parvovirus B19 is the causative agent of fifth disease (erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intense erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and occur in the spring of the year. Close contact between individuals is responsible for infection in schools, daycare centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia.

Infection during pregnancy risks transmission to the fetus, which may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%.

**Useful For:** Diagnosing recent parvovirus infection (IgM) Assessing past infection (eg, screening pregnant women) and immunity to parvovirus infection (IgG)

**Interpretation:** Specimens with an index of <0.9 are considered negative. Specimens with an index of >1.1 are considered positive. Specimens with an index between 0.9 and 1.1, inclusive, are considered equivocal. Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative Implies no past infection/patient may be susceptible to B19V infection/positive Implies past exposure/infection-minimal risk of B19V infection Equivocal Positive or negative May indicate current or recent B19V infection-retest in 1 to 2 weeks Positive Positive Implies past current or recent B19V infection Positive Negative or equivocal May indicate current B19V infection-retest in 1 to 2 weeks The presence of IgM class antibodies indicates recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older).

**Reference Values:**

IgG: <0.9
IgM: <0.9


**Parvovirus B19, Molecular Detection, PCR**

**Clinical Information:** Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults.(1) Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host.(2,3) Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus.(4) Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients, transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

**Useful For:** Diagnosing parvovirus B19 infection

**Interpretation:** A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or simply the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

**Reference Values:**

Negative


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**Parvovirus B19, Molecular Detection, PCR, Plasma**

**Clinical Information:** Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults.(1) Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver, depending on the immune competence of the host.(2,3) Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus.(4) Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients, transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

**Useful For:** Diagnosing parvovirus B19 infection in plasma specimens

**Interpretation:** A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or simply the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1516

PAS Diastase Stain (Bill Only)
Reference Values:
This test is for billing purposes only.
This test is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

Passion Fruit, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

Pathology Consultation

Clinical Information: Mayo Clinic Rochester is staffed by pathologists whose expertise and special interests cover the entirety of pathology—from surgical pathology with all of its respective subspecialty areas, to Hematopathology, Renal Pathology, and Dermatopathology. We provide consultation services on difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and sometimes transferred between the pathologists, as deemed appropriate for the type of case or diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Stained slides and paraffin blocks received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist’s report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogentic, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. It is our goal to provide the highest possible level of diagnostic consultative service, while trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

Useful For: Obtaining a rapid, expert second opinion on specimens referred by the primary pathologist

Obtaining special studies not available locally

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results are communicated by a phone call. The formal pathology report is faxed. In our consultative practice, we strive to bring the customer the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

PCA3 Assay

Clinical Information: Background: PCA3 is a non-coding prostate-specific mRNA that is highly over-expressed in some prostate cancer cells (median 66-fold over adjacent benign tissue); in contrast, PSA gene expression is similar in benign and malignant prostate cells. Both PCA3 and PSA mRNA can be quantitated from urine samples. The PCA3 assay utilizes voided urine collected following a digital rectal examination and processed by addition into a urine transport medium (UTM) which lyses cells and stabilizes RNA. The PSA mRNA level serves to confirm that there is sufficient prostate RNA for analysis present in the sample and to normalize the PCA3 mRNA signal. In a study of 466 patients with previous negative prostate biopsy, 102 of whom had a positive follow-up biopsy, utilizing the PCA3 score cutoff value of 25 was shown to have 77.5% sensitivity and 57.1% specificity for prostate cancer. This assay is indicated for use in conjunction with other patient information to aid in the decision of repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, before consideration of the PCA3 assay results. This assay should not be used for men with atypical small acinar proliferation (ASAP) on their most recent biopsy; men with ASAP on their most recent biopsy should be treated in accordance with current medical guidelines. PCA3 score interval Number of subjects Percent of subjects with Positive Biopsy <12 114 10% 12-<25 117 12% 25-<47 116 28% 47+ 119 35% This figure shows the percentage of subjects with positive biopsy results by PCA3 score interval.

Reference Values:

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Reference Range:
- <25 negative
- > or = 25 positive

Comment: Due to normal assay variability, specimens with PCA3 scores near the cut-off of 25 (i.e. 18-31) could yield a different overall interpretation of positive or negative upon repeat testing. PCA3 scores in the range from 18 to 31 should, therefore, be interpreted with caution.

The testing method is target capture, transcription-mediated amplification (TMA) and hybrid protection assay (HPA), manufactured by Gen-Probe and performed using the Gen-Probe PROGENSA assay kit.


88725 PD-L1 (B7-H1, CD274), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Programmed cell death 1 ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

Useful For: Identification of neoplasms expressing programmed cell death 1 ligand 1

Interpretation: This test will be answered as percent tumor cells positive or negative and immune cells positive or negative. If additional interpretation or analysis is needed, request test 70012 / Pathology Consultation along with this test.


PDGF

PDGFB (22q13), Dermatofibrosarcoma Protuberans/Giant Cell Fibroblastoma, FISH, Tissue

Clinical Information: Dermatofibrosarcoma protuberans (DFSP) is a superficial, low-grade sarcoma genetically characterized by the unbalanced chromosomal translocation t(17;22)(q21;q13), usually in the form of a supernumerary ring chromosome. The product of this chromosomal translocation is the chimeric gene COL1A1-PDGFB. Rearrangements of this gene have been detected in approximately 90% of DFSP and its related infantile form, giant cell fibroblastoma, but not in other tumors.

Useful For: Confirming the diagnosis of dermatofibrosarcoma protuberans (DFSP)/giant cell fibroblastoma (GCF) and excluding other spindle neoplasms that closely simulate the DFSP histology, including dermatofibroma (benign fibrous histiocytoma), neurofibroma, spindle cell lipoma, and a variety of other benign and malignant spindle cell neoplasms
Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the PDGFB FISH probe. A positive result is consistent with rearrangement/amplification of the PDGFB gene locus on 22q13 and supports the diagnosis of dermatofibrosarcoma protuberans (DFSP) or giant cell fibroblastoma (GCF). A negative result is consistent with no rearrangement/amplification of the PDGFB gene locus on 22q13. However, this result does not exclude the diagnosis of DFSP or GCF. The degree of PDGFB copy gain/amplification/rearrangement varies in individual tumors and among different cells in the same tumor. It is not currently known if patients with different levels of rearrangement/amplification have the same prognosis and response to therapy.

Reference Values:
An interpretive report will be provided.


**PDGFRA Exon 12, Mutation Analysis**

Clinical Information: Occasional cases of gastrointestinal stromal tumors (GIST) can harbor mutations in PDGFRA, a gene structurally related to KIT. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

Useful For: Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 12 of the PDGFRA gene

Interpretation: Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

Reference Values:
An interpretive report will be provided.


**PDGFRA Exon 14, Mutation Analysis**

Clinical Information: Occasional cases of gastrointestinal stromal tumors (GIST) can harbor mutations in PDGFRA, a gene structurally related to KIT. The frequency and type of mutations vary...
among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other tumors Identification of a mutation in exon 14 of the PDGFRA gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**PDGFRA Exon 18, Mutation Analysis**

**Clinical Information:** Occasional cases of gastrointestinal stromal tumors (GIST) can harbor mutations in PDGFRA, a gene structurally related to KIT. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 18 of the PDGFRA gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
PDGFRB/TEL Translocation (5;12) for Chronic Myelomonocytic Leukemia (CMML), FISH

**Clinical Information:** Platelet-derived growth factor receptor-beta (PDGFRB) produces a tyrosine kinase involved in cell proliferation. Translocation-ets-leukemia protein (encoded by the gene ETV6) is a gene transcription protein that is frequently rearranged in leukemias. A 5;12 translocation, t(5;12)(q33;p13), results in a fusion product (PDGFRB/ETV6) that is seen in approximately 1% to 2% of patients diagnosed with chronic myelomonocytic leukemia. Patients with this translocation often have associated hypereosinophilia. Imatinib mesylate is an inhibitor of tyrosine kinases, including PDGFRB. Patients with the 5;12 translocation are reportedly responsive to imatinib mesylate; upon treatment, they usually go into complete remission.

**Useful For:** Identifying patients with chronic myelomonocytic leukemia and other hematologic disorders who may be responsive to imatinib mesylate Identifying and tracking chromosome abnormalities and response to therapy

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Pea Black-Eyed/Cow Pea (Vigna sinensis) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Pea Green IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Peach IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**PECH 82816**

**Peach, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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<td>&lt;0.10</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**FPCP 58010**

**Peanut Component Panel**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline
Reference Values:
<0.35 kU/L

**FPNTG**

**Peanut IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FPNG4**

**Peanut IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

Reference Values:
<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**PEAN**

**Peanut, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


**FPEAR 57683**

**Pear IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**PEAR 82807**

**Pear, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
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<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Pecan Food IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Pecan Hickory, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and defining the allergens responsible for eliciting signs and symptoms. Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, confirming sensitization to particular allergens prior to beginning immunotherapy, and investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical
Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>IgE kU/L</th>
<th>Interpretation</th>
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<tr>
<td>0</td>
<td></td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


PEC 82880

Pecan-Food, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Pediatric Allergy Screen 3 to 8 Years, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.

Pediatric Allergy Screen

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<td>2</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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Pediatric Allergy Screen >8 Years, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Interpretation</th>
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<tbody>
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<td></td>
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<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Penicillin G, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
### Penicillin V, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.
**Penicillium chrysogenum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.

pressure that may follow stroke or head trauma. Pentobarbital is administered orally, parenterally, and rectally. The duration of hypnotic effect is about 1 to 4 hours. The drug distributes throughout the body, with about 35% to 45% of a dose bound to plasma proteins in the blood. Metabolism takes place in the liver via oxidation to the inactive metabolite hydroxypentobarbital. Elimination is biphasic; half-life is about 4 hours in the first phase, and 35 to 50 hours in the second phase. Excretion occurs through the urine, mainly as glucuronide conjugates of metabolites, with only about 1% excreted as unchanged drug. Tolerance to pentobarbital's hypnotic effects occurs after about 2 weeks of continuous dosing.

**Useful For:** Monitoring of pentobarbital therapy treatment

**Interpretation:** Therapeutic range (3) Hypnotic: 1 to 5 mcg/mL Therapeutic coma: 20 to 50 mcg/mL Reducing intracranial pressure: 30 to 40 mcg/mL - This degree of sedation requires artificial respiratory support. Toxic: >10 mcg/mL - The concentration at which toxicity occurs varies; results should be interpreted in light of clinical situation.

**Reference Values:**
Therapeutic range
- Hypnotic: 1-5 mcg/mL
- Therapeutic coma: 20-50 mcg/mL
- Reducing intracranial pressure: 30-40 mcg/mL
  
  This degree of sedation requires artificial respiratory support.
  
  Toxic concentration: >10 mcg/mL
  
  The concentration at which toxicity occurs varies; results should be interpreted in light of clinical situation.


**FPBPG 57657**  
**Pepper Bell/Paprika IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FPBLG 57645**  
**Pepper Black IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Pepper Cayenne (Capsicum frutescens) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Pepper Chili IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Pepsin A Assay

**Reference Values:**
Protein Unit = mg/mL
One unit of pepsin A = 0.1 ng/mL
Pepsin A by Elisa assay

Pepsin A Reference Range (Units):
<3.0 negative
3-50 weak to moderate positive
>50 strong positive

Pepsinogen I

**Reference Values:**
28 - 100 ng/mL
(mean 40)

Perch Ocean

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Percocet, Urine
### Reference Values:

**Percocet, Urine:**  
Acetaminophen: ug/mL  
Note: Analysis performed on urine.

Reference ranges have not been established for urine specimens.

Oxycodone: ng/mL  
Oxymorphone: ng/mL

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### PASS 80867

**Periodic Acid-Schiff Stain (Bill Only)**

**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

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### NPPC 63084

**Peripheral Nerve Pathology Consultation**

**Clinical Information:** Nerve biopsies provide information about nerve fibers and the interstitium of the nerve. Neuropathic abnormalities include decreased density of myelinated fibers, segmental demyelination, and axonal degeneration. Some possible interstitial abnormalities that affect nerves include necrotizing vasculitis and amyloidosis.

**Useful For:** Evaluating diseases of the nerve and disorders that affect nerve function. This consultation is for fixed tissue, slides, or blocks.

**Interpretation:** The clinical and neurological history is reviewed with the interpretation of the biopsy. The histologic slides, special stains, and history, along with the physician's report are correlated by a neuromuscular pathologist. An interpretive report will be provided.

**Reference Values:**  
An interpretive report will be provided.

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### PNPAN 64358

**Peripheral Neuropathy Expanded Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement: 1) hereditary motor and sensory neuropathy (HMSN), also referred as Charcot Marie Tooth (CMT); 2) hereditary sensory and autonomic neuropathy (HSAN), or hereditary sensory neuropathy (HSN), if autonomic dysfunction is absent; and 3) distal hereditary motor neuropathy (dHMN). Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as in hereditary spastic paraplegia (HSP) with neuropathy (complicated form, also referred to as HSMN type 5) or be part of a systemic syndromic or metabolic disorder. Given the considerable phenotypic overlap and the broad genetic heterogeneity of inherited peripheral neuropathies a comprehensive diagnostic genetic test is useful to establish the genetic cause in these clinical groups. The recommended first-tier test to screen for hereditary motor and sensory neuropathy is PMP22 /
PMP22, Peripheral Neuropathy, FISH, which assess for large deletions and duplications of the PMP22 gene. See Targeted Genes Interrogated by Peripheral Neuropathy Expanded Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosis of inherited peripheral neuropathies with isolated nerve involvement or associated with other organ system or associated with metabolic syndromes with known causal genes A second-tier test for patients in which previous targeted gene mutation analyses for specific inherited peripheral neuropathy-related genes were negative Identifying mutations within genes known to be associated with inherited peripheral neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Peripheral T-Cell Lymphoma (PTCL), TP63 (3q28) Rearrangement, FISH, Tissue**

**Clinical Information:** Peripheral T-cell lymphomas (PTCL) are malignant neoplasms of mature T-lymphocyte origin that account for 10% to 15% of all non-Hodgkin lymphomas. Most subtypes have a slight male predominance and occur in older individuals (>50 years). Some subtypes, particularly ALK-positive anaplastic large cell lymphoma (ALCL), are seen in younger patients. Over 15 subtypes of PTCL are recognized in the World Health Organization classification system. These types differ in their clinical presentation, morphologic appearance, immunophenotype, genetics, and in some cases, prognostic and therapeutic implications. The relative distribution of subtypes varies geographically. In the United States, the most common types of systemic PTCL are PTCL, not otherwise specified (NOS); angioimmunoblastic T-cell lymphoma (AITL); and ALCL (both ALK-positive and ALK-negative types). In diagnostic practice, PTCL must be distinguished from reactive T-cell proliferations as well as from hematopoietic neoplasms of non-T-cell lineage and nonhematopoietic tumors. In addition, PTCL must be subclassified to the extent possible. The designation PTCL, NOS, is reserved for PTCL that do not meet criteria for inclusion in one of the other, more specific categories, which occurs in a significant fraction of PTCL. Recurrent translocations involving the TP63 gene on 3q28 have been described in PTCL. In one series of 190 PTCL of various subtypes, TP63 translocations were seen in 5.8%. However, these were not distributed equally among PTCL subtypes, occurring in 9.4% of PTCL, NOS; 12.5% of ALK-negative ALCL; and 10.5% of primary cutaneous ALCL. No cases of ALK-positive ALCL, AITL, or other PTCL subtypes were found to have TP63 translocations. In 63.6% of cases with TP63 translocations, the translocation partner gene was identified to be TBL1XR1. Other partners also exist. TP63 translocations have been shown to encode fusion transcripts that give rise to fusion proteins homologous to delta-N isoforms of wild-type p63. In 1 study, the presence of TP63 translocations among PTCL was associated with inferior overall survival compared with PTCL without TP63 translocations (median survival: 17.9 months vs. 33.4 months, respectively; p<0.05). The clinical significance of the presence of a variant (non-TBL1XR1) partner is not known. Immunohistochemical staining for p63 protein with the 4A4 clone can be seen in cases without TP63 translocations, did not demonstrate prognostic significance in 1 study, and should not be considered a surrogate for TP63 translocation testing. TP63 translocations also have been identified in some B-cell non-Hodgkin lymphomas. Thus, the presence of a TP63 translocation should not be considered diagnostic for PTCL, and this result should be interpreted in the context of other
pathologic, immunophenotypic, genetic, and clinical data. The clinical utility of TP63 testing in B-cell lymphomas has not been established.

**Useful For:** Supporting the diagnosis of peripheral T-cell lymphoma when coordinated with a consultation by anatomic pathology

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff of the TP63 probe sets. Among peripheral T-cell lymphomas, translocations involving TP63 have been associated with aggressive clinical behavior. B-cell lymphomas also may demonstrate this finding. Clinical and pathologic correlation is recommended.

**Reference Values:**
An interpretive report will be provided.


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**ACASM Pernicious Anemia Cascade**

**Clinical Information:** Vitamin B12 deficiency can be caused by many factors, one of which is pernicious anemia, a condition resulting in deficient production of intrinsic factor in the parietal cells of the stomach. Intrinsic factor is a protein that is needed to assist in the absorption of vitamin B12 into the small intestine. Vitamin B12 is converted into adenosylcobalamin, which converts L-methylmalonic acid to succinyl coenzyme A; hence, a decrease in vitamin B12 absorption in the intestine can cause an excess of methylmalonic acid within the body. Vitamin B12 deficiency may present with any combination of the following: macrocytic anemia, glossitis (painful inflammation of the tongue), peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients present with neurologic symptoms without macrocytic anemia. A group of tests is often required to establish the correct diagnosis as determination of vitamin B12 in serum does not detect all cases of vitamin B12 deficiency. Mayo Clinic's Department of Laboratory Medicine and Pathology offers a diagnostic algorithm to expedite the identification of patients with vitamin B12 deficiency. This algorithm takes into account the following facts: -The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for methylmalonic acid (MMA). -Nearly half of the cases of pernicious anemia can be unambiguously identified if the serum test for intrinsic factor blocking antibody is positive (this is a simpler and less expensive test than the MMA). -Serum gastrin is usually markedly increased in pernicious anemia (as a result of gastric atrophy) and this test can be used as a substitute for the more complicated and more expensive Schilling test of intestinal absorption of vitamin B12. The algorithm is similar to that published by Green,(1) except that the serum gastrin assay is performed in place of the Schilling test. Experience with both Mayo Clinic and Mayo Medical Laboratories' cases has corroborated that this is a cost-effective alternative to the Schilling test. In our experience, >90% of laboratory test costs can be saved by using the algorithm rather than ordering all of the services for a patient suspected of having B12 deficiency. Furthermore, the substitution of the serum gastrin assay for the Schilling test offers 3 advantages: 1. It is an in vitro test that does not require administration of radioisotopes to patients 2. It can be performed on mailed-in specimens 3. It is much less expensive Only those tests that are appropriate, as defined by the algorithm, will be performed.

**Useful For:** Diagnosis of pernicious anemia Diagnosis of vitamin B12 deficiency-associated neuropathy

**Interpretation:** Vitamin B12 >400 ng/L. Results do not suggest B12 deficiency-no further testing. Vitamin B12 150 to 400 ng/L. Borderline vitamin B12 level-methylmalonic acid (MMA) is performed. If MMA is >0.40 nmol/mL, then intrinsic factor blocking antibody (IFBA) is performed. Vitamin B12 <150 ng/L. Vitamin B12 deficiency-IFBA is performed. If IFBA is negative or indeterminate, then gastrin is performed. MMA < or =0.40 nmol/mL This value implies that there is no vitamin B12 deficiency at the cellular level. IFBA positive consistent with pernicious anemia, Graves disease, or Hashimoto thyroiditis. Gastrin >200 pg/mL. Result consistent with pernicious anemia. Gastrin <200 pg/mL. Result does not
suggest pernicious anemia. See Vitamin B12 Deficiency Evaluation in Special Instructions.

**Reference Values:**
180-914 ng/L


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**Perphenazine, (Trilafon), Serum**

**Reference Values:**
Reference Range: 5.0 - 30.0 ng/mL

Low-dose therapeutic range for Perphenazine: 0.5 - 2.5 ng/mL

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**Persimmon, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>
| 6     | > or =100 | Strongly positive Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and Current as of July 8, 2016 11:28 am CDT
Clinical Information: Urine pH is a measure of the acidity/alkalinity of urine and by itself usually provides little useful information. Under normal conditions its value is influenced by the type of diet. Some diets (eg, diets rich in meat) have more acid content than others (eg, vegetarian diets). Changes in urine pH may reflect systemic acid-base disorders. For example, the normal response during metabolic acidosis is a lowering of the urine pH to <5. If the pH is >5, then a defect in urine acidification should be considered. A urine pH >7 is suggestive of infection by a urea-splitting organism such as Proteus mirabilis. Therapeutic interventions to either alkalinate or acidify the urine are necessary for some diseases. For example, some crystals have a propensity to form in alkaline urine, while others form in relative acidic urine, and changing the pH may reduce stone formation.

Useful For: Assessment of patients with metabolic acidosis Assessment of crystalluria Monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis)

Interpretation: Dependent on clinical condition A pH >7 suggests the presence of urinary tract infection with a urea-splitting organism.

Reference Values: 4.5-8.0

Clinical Information: The pH value is a measure of hydrogen ion concentration. A variety of disease processes can alter pH values. Determining the pH value of a body fluid may help characterize the nature of the fluid.

Useful For: Gastric fluid pH can help determine if acid production in the stomach is normal.

Interpretation: Normal gastric fluid has a pH <3.5; any higher pH is abnormal.

Reference Values: Varies with fluid type and location.


Clinical Information: Urine pH is a measure of the acidity/alkalinity of urine, and by itself usually

Reference Values: 5.0 - 8.5
provides little useful information. Under normal conditions its value is influenced by the type of diet (some diets: eg, diets rich in meat-having more acid content than others; eg, vegetarian diets). Assessment of urine pH may be useful in the evaluation of systemic acid-base disorder. For example, the normal response during metabolic acidosis is a lowering of the urine pH to less than 5. If it is >5, then a defect in urine acidification should be considered. Often a urine pH above 7 is suggestive of infection of a urea splitting organism such as proteus mirabilis. Monitoring of urine pH may also be helpful during therapeutic interventions to either alkalinate the urine (such as for treatment of uric acid nephrolithiasis) or acidify the urine. Finally, when assessing crystalluria, noting the urine pH may be helpful since some crystals have a propensity to form in alkaline urine while others form in relative acidic urine.

**Useful For:** Assessment of patients with metabolic acidosis Assessment of crystalluria Monitoring the effectiveness of alkalination or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis)

**Interpretation:** Dependent on clinical condition.

**Reference Values:**
N/A

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**FPHAS 57580 Phadiatop (Allergy Screen)**

**Reference Values:**
Negative

The Phadia Phadiatop test is an allergy screening test with excellent sensitivity and specificity for inhalant allergy. It uses an ImmunoCAP with a balanced mixture of representative allergens, including grasses, trees, weeds, cat, dog, mites and molds. A positive result indicates that the patient is allergic to one or more of these allergens; a negative indicates the patient is not allergic to inhalant allergens. Note that the test does not assess a patient’s sensitivity to food, drug, chemical or certain unusual or rare allergens.

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**PCPEG 9788 Phencyclidine (PCP), Confirmation, serum**

**Reference Values:**
Toxic: Greater than 100 ng/mL
Serious Toxicities likely: Greater than 300 ng/mL

**PCPMX 62740 Phencyclidine Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles.(1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors.(1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects.(1,2) PCP is approximately 65% protein bound and has a volume of distribution (Vd) of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours.(2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct
deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth

**Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.** Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of phencyclidine in meconium is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

- **Negatives** are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**

- PCP by LC-MS/MS: 10 ng/g

**Clinical References:**


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**Phencyclidine Confirmation, Chain of Custody, Urine**

**Clinical Information:** Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotonergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, giving bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screen. PCP is excreted in the urine. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of drug abuse involving phencyclidine (angel dust or angel hair). Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of phencyclidine (PCP) in urine at concentrations >10 ng/mL is a strong indicator that the patient has used PCP.

**Reference Values:**

- **Negatives**

**Cutoff concentrations**
**Phencyclidine Confirmation, Meconium**

**Clinical Information:** Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles. (1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors. (1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects. (1, 2) PCP is approximately 65% protein bound and has a volume of distribution (Vd) of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours. (2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. (3) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. (4) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. (3)

**Useful For:** Detection of in utero drug exposure up to 5 months before birth

**Interpretation:** The presence of phencyclidine in meconium is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - PCP by LC-MS/MS: 10 ng/g

**Clinical References:**

Phencyclidine Confirmation, Urine

Clinical Information: Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotoninergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, giving bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screen. PCP is excreted in the urine.

Useful For: Detection of drug abuse involving phencyclidine (angel dust or angel hair)

Interpretation: The presence of phencyclidine (PCP) in urine at concentrations >10 ng/mL is a strong indicator that the patient has used PCP.

Reference Values:
Negative
Cutoff concentrations
Phencyclidine by GC-MS: <10 ng/mL


Phenelzine, Serum/Plasma

Reference Values:
Reporting limit determined each analysis

Synonym(s): Nardil

Reported serum levels from patients on therapeutic doses are normally in the range of 1 - 100 ng/mL.

Phenobarbital, Serum

Clinical Information: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex partial seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations >40.0 mcg/mL. Symptoms become severe at concentrations > or =60.0 mcg/mL. Toxicity becomes life-threatening at concentrations >100.0 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

Useful For: Monitoring for appropriate therapeutic concentration of phenobarbital Assessing compliance or toxicity
**Interpretation:** Clinical response to the drug correlates strongly with blood concentration. Dosage adjustments are made after 2 weeks of therapy to achieve steady-state blood levels in the range of 20.0 to 40.0 mcg/mL for adults; 15.0 to 30.0 mcg/mL for infants and children. Patients chronically administered phenobarbital usually do not experience sedation unless the blood concentration is >40.0 mcg/mL.

**Reference Values:**
Therapeutic: 10.0-40.0 mcg/mL
Critical value: > or =60.0 mcg/mL


**Phenosense Combination HIV Drug Resistance Assay**

**FPGT 91757**

**Reference Values:**
A final report will be attached in MayoAccess.

**Phenosense Entry HIV Drug Resistance Assay**

**FPFUZ 91755**

**Reference Values:**
A final report will be attached in MayoAccess.

**Phenosense HIV Drug Resistance Replication Capacity**

**FPHIV 91756**

**Reference Values:**
A final report will be attached in MayoAccess.

**Phenylalanine and Tyrosine, Plasma**

**PKU 8380**

**Clinical Information:** Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Thyroxine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalanemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of not only PAH, but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalanemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalanemia: guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterine synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, seizures, and mental retardation though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that derives from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

**Useful For:** Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia
Interpretation: The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

Reference Values:

PHENYLALANINE
- Premature: 98-213 nmol/mL
- 0-31 days: 38-137 nmol/mL
- 1-24 months: 31-75 nmol/mL
- 2-18 years: 26-91 nmol/mL
- > or =19 years: 35-85 nmol/mL

Conversion Formulas:
Result in mg/dL x 60.6 = result in nmol/mL
Result in nmol/mL x 0.0165 = result in mg/dL

TYROSINE
- Premature: 147-420 nmol/mL
- 0-31 days: 55-147 nmol/mL
- 1-24 months: 22-108 nmol/mL
- 2-18 years: 24-115 nmol/mL
- > or =19 years: 34-112 nmol/mL

Conversion Formulas:
Result in mg/dL x 55.6 = result in nmol/mL
Result in nmol/mL x 0.0181 = result in mg/dL

See Inborn Errors of Amino Acid Metabolism in Special Instructions.


**PDNS**

81101  Phenylenediamine, Nrv ST

Reference Values:
Report sent under separate cover

**PNYF**

37052  Phenytoin, Free, Serum

Clinical Information: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Phenytoin is highly protein-bound (90%), mostly to albumin. Ten percent of the phenytoin circulates in the free, unbound form. Free phenytoin is the active form of the drug, available to cross biologic membranes and bind to receptors. Increased free phenytoin produces an enhanced pharmacologic effect. At the same time, the free fraction is more available to the liver to be
metabolized, so it is cleared more quickly. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma.

**Useful For:** Monitoring for appropriate therapeutic concentration of free phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure Assessing compliance and toxicity

**Interpretation:** Dose should be adjusted to achieve steady-state blood concentration of free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. Severe toxicity occurs when the free phenytoin concentration is > or =2.5 mcg/mL. However, response and side effects will be individual.

**Reference Values:**
Therapeutic: 1.0-2.0 mcg/mL. Critical value: > or =2.5 mcg/mL

**Clinical References:** Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169

**Phenytoin, Total and Free, Serum**

**Clinical Information:** Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. Phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage
must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

**Useful For:** Monitoring for appropriate therapeutic concentration of both free and total phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure

**Interpretation:** Dose should be adjusted to achieve steady-state concentrations of total phenytoin between 10.0 and 20.0 mcg/mL, and free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. However, response and side effects will be individual. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

**Reference Values:**

**Phenytoin, Total**
- Therapeutic: 10.0-20.0 mcg/mL
- Critical value: > or =30.0 mcg/mL

**Phenytoin, Free**
- Therapeutic: 1.0-2.0 mcg/mL
- Critical value: > or =2.5 mcg/mL

**Clinical References:**

**Phenytoin, Total and Phenobarbital Group, Serum**

**Clinical Information:** Phenytoin, Total: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin which causes an increase in the free fraction. Valproic acid, an antiepileptic frequently coadministered with phenytoin, competes for the same binding sites on albumin as phenytoin. Valproic acid displaces phenytoin from albumin, reducing the bound fraction and increasing the free fraction. The overall effect of coadministration of a therapeutic dose of valproic acid is that the total concentration of phenytoin decreases due to increased clearance but the free fraction increases; the free concentration of phenytoin, which is the active form remains virtually the same. Thus, no dosage adjustment is needed when valproic acid is added to maintain the same pharmacologic effect, but the total concentration of phenytoin decreases. In contrast to the valproic acid.
situation, in renal failure, there is not the same opportunity for the free phenytoin fraction to be cleared. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. The free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is >30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative. Phenobarbital: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex partial seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations >40 mcg/mL. Symptoms become severe at concentrations > or =60 mcg/mL. Toxicity becomes life-threatening at concentrations >100 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

**Useful For:** Monitoring for appropriate therapeutic concentration of phenytoin and phenobarbital Assessing compliance or toxicity

**Interpretation:** The therapeutic ranges for adults taking phenytoin have been established at 10 to 20 mcg/mL for total phenytoin (bound plus unbound). The therapeutic range for phenobarbital is 10 to 40 mcg/mL. Within these ranges, most people will respond to the drugs without symptoms of toxicity. However, response and side effects will be individual. Dosage determinations and adjustments must be evaluated on a case-by-case basis. A free (unbound) phenytoin level may also need to be ordered when a person has kidney failure, liver disease, hypoalbuminemia, or is taking other medications like aspirin, naproxen, or ibuprofen, in which situation the percentage of free (active) phenytoin may be increased.

**Reference Values:**

**PHENYTOIN, TOTAL**

- Therapeutic: 10.0-20.0 mcg/mL
- Critical value: > or =30.0 mcg/mL

**PHENOBARBITAL**

- Therapeutic: 10.0-40.0 mcg/mL
- Critical value: > or =60.0 mcg/mL


**Phenytoin, Total, Serum**

**Clinical Information:** Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order
(nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy in renal failure. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is >30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

**Useful For:** Monitoring for appropriate therapeutic concentration Assessing compliance or toxicity

**Interpretation:** Dose should be adjusted to achieve steady-state total phenytoin concentrations between 10.0 and 20.0 mcg/mL. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

**Reference Values:**
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL


**PHMA 82736**

**Phoma betae, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or = 100</td>
</tr>
</tbody>
</table>


**Phosphatidylglycerol Antibodies, IgG, IgM and IgA**

**Reference Values:**

**Phosphatidylglycerol Antibody, IgG:**

<table>
<thead>
<tr>
<th>Level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 â€“ 11 U/ml:</td>
<td>Normal</td>
</tr>
<tr>
<td>12 â€“ 18 U/ml:</td>
<td>Equivocal. Suggest repeat testing in 4 â€“ 6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.</td>
</tr>
<tr>
<td>19 U/ml or greater:</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Phosphatidylglycerol Antibody, IgM:**

<table>
<thead>
<tr>
<th>Level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 â€“ 11 U/ml:</td>
<td>Normal</td>
</tr>
<tr>
<td>12 â€“ 18 U/ml:</td>
<td>Equivocal. Suggest repeat testing in 4 â€“ 6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.</td>
</tr>
<tr>
<td>19 U/ml or greater:</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Phosphatidylglycerol Antibody, IgA:**

<table>
<thead>
<tr>
<th>Level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 â€“ 11 U/ml:</td>
<td>Normal</td>
</tr>
<tr>
<td>12 â€“ 18 U/ml:</td>
<td>Equivocal. Suggest repeat testing in 4 â€“ 6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.</td>
</tr>
<tr>
<td>19 U/ml or greater:</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Phosphatidylinositol Antibodies, IgG, IgM and IgA

Reference Values:
- Phosphatidylinositol Antibody IgG (0 – 18) U/mL
- Phosphatidylinositol Antibody IgM (0 – 18) U/mL
- Phosphatidylinositol Antibody IgA (0 – 18) U/mL

- 0 â€“ 11 u/mL: Normal
- 12 â€“ 18 u/mL: Equivocal. Suggest repeat testing in 4 â€“ 6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.
- 19 or greater u/mL: Positive

Phosphatidylserine Antibodies, IgG, IgM, IgA

Reference Values:
- Phosphatidylserine Antibody IgG (0-10) U/mL
- Phosphatidylserine Antibody IgM (0-24) U/mL
- Phosphatidylserine Antibody IgA (0-19) U/mL

Phosphofructokinase Stain

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

Phospholipase A2 Receptor (PLA2R) Frozen IF, Renal

Clinical Information: Membranous nephropathy is the most common cause of nephrotic syndrome in white adults. Eighty-five percent of membranous nephropathy cases are primary or idiopathic and the other 15% are secondary. Phospholipase A2 receptor (PLA2R) is an antigen located on podocytes. The majority of cases of primary membranous nephropathy have circulating autoantibodies against PLA2R.

Useful For: Distinguishing primary membranous nephropathy from secondary membranous nephropathy

Interpretation: This test, (when not accompanied by a pathology consultation request) will be reported as either positive or negative. If additional interpretation/analysis is needed, request 70012 / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.


Phospholipase A2 Receptor (PLA2R) Immunofluorescent Stain, Renal
Membranous nephropathy is the most common cause of nephrotic syndrome in white adults. Eighty-five percent of membranous nephropathy cases are primary/idiopathic and the other 15% are secondary. Phospholipase A2 receptor (PLA2R) is an antigen located on podocytes. The majority of cases of primary membranous nephropathy have circulating autoantibodies against PLA2R.

Distinguishing primary membranous nephropathy from secondary membranous nephropathy

This test (when not accompanied by a pathology consultation request) will be reported as either positive or negative. If additional interpretation/analysis is needed, please request 70012 / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.


Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor (PLA2R) antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

ELISA:
- Negative: <14 RU/mL
- Borderline: or =14-<20 RU/mL
- Positive: or =20 RU/mL

IFA: Negative

Phospholipase A2 Receptor, Indirect Immunofluorescence Assay, Serum

**Scope**

Phospholipase A2 Receptor Antibodies, Serum

**Reference Values:**

For more information see PLA2R / Phospholipase A2 Receptor Antibodies, Serum.

**ACLIP**

Phospholipid (Cardiolipin) Antibodies, IgA, Serum

**Clinical Information:** The plasma membranes of mammalian cells are formed from phospholipids.

Anionic phospholipids (e.g., phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (e.g., phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2 glycoprotein 1 (beta 2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta 2 GP1. Beta 2 GP1 is a 326 amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. Only those phospholipid antibodies that are capable of cross-linking beta 2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta 2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM anti-beta 2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anti-cardiolipin and anti-beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

**Useful For:** Evaluation of suspected cases of antiphospholipid syndrome

**Interpretation:** APL, GPL and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the
The abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype (APL) may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA phospholipid (cardiolipin) antibody results >15 APL with negative IgG and IgM phospholipid (cardiolipin) antibody results are not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <10.0 APL (negative)
- 10.0-14.9 APL (borderline)
- 15.0-39.9 APL (weakly positive)
- 40.0-79.9 APL (positive)
- > or =80.0 APL (strongly positive)

APL refers to IgA Phospholipid Units. One APL unit is 1 microgram of IgA antibody.

Reference values apply to all ages.

**Clinical References:**

**CLPMG 82976 Phospholipid (Cardiolipin) Antibodies, IgG and IgM, Serum**

**Clinical Information:** The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (eg, phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (eg, phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2 glycoprotein 1 and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta 2 glycoprotein 1 (beta 2 GP1). Beta 2 GP1 is a 326 amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro. Not all phospholipid antibodies possess lupus anticoagulant activity.
phospholipid antibodies that are capable of cross-linking beta 2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta 2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Phospholipid antibodies occur in patients with a variety of clinical signs and symptoms notably thrombosis (arterial or venous) pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency) unexplained cutaneous circulation disturbances (livido reticularis or pyoderma gangrenosum) thrombocytopenia or hemolytic anemia and nonbacterial thrombotic endocarditis. Phospholipid antibodies and lupus anticoagulants are found with increased frequency in patients with systemic rheumatic diseases especially lupus erythematosus. The term antiphospholipid syndrome (APS) or Hughes’ syndrome is used to describe the triad of thrombosis, recurrent fetal loss and thrombocytopenia accompanied by phospholipid antibodies or a lupus anticoagulant. The diagnosis of APS requires 1 or more of the above mentioned clinical findings plus positive test results for phospholipid antibodies (> or =40 GPL or MPL) or positive tests for a lupus anticoagulant on more than 1 occasion separated by at least 6 weeks.(4)

**Useful For:** Testing for phospholipid antibodies is indicated in the following clinical situations:
- Unexplained arterial or venous thrombosis
- A history of pregnancy morbidity defined as 1 or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, 1 or more premature births before 34 weeks of gestation caused by severe preeclampsia or placental insufficiency, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation with no identifiable maternal hormonal or anatomic, or maternal or paternal chromosomal causes
- Presence of an unexplained cutaneous circulatory disturbance, eg, livido reticularis or pyoderma gangrenosum
- Presence of a systemic rheumatic disease especially lupus erythematosus
- Unexplained thrombocytopenia or hemolytic anemia
- Possible nonbacterial, thrombotic endocarditis

**Interpretation:** Positive and strongly positive results for phospholipid antibodies (> or =40 GPL and/or MPL) are a diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of phospholipid antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Detection of phospholipid antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <10.0 MPL or GPL (negative)
- 10.0-14.9 MPL or GPL (borderline)
- 15.0-39.9 MPL or GPL (weakly positive)
- 40.0-79.9 MPL or GPL (positive)
- > or =80.0 MPL or GPL (strongly positive)

MPL refers to IgM Phospholipid Units. One MPL unit is 1 microgram of IgM antibody. GPL refers to IgG Phospholipid Units. One GPL unit is 1 microgram of IgG antibody. Reference values apply to all ages.

**Clinical References:**
phospholipids (eg, phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes.(1) Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies.(2) Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2 glycoprotein 1 (beta 2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta 2 GP1. Beta 2 GP1 is a 326 amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anti-coagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anti-coagulant activity.(3) Only those phospholipid antibodies that are capable of cross-linking beta 2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta 2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met.(4) The clinical criteria include vascular thrombosis (artrial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anti-coagulant, presence of IgG and/or IgM antcardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM anti-beta 2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anti-cardiolipin and beta GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.(4) Useful For: Evaluation of suspected cases of antiphospholipid syndrome Interpretation: APL, GPL, and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters “PL” denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL, and/or >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM anti-beta 2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anti-cardiolipin and beta GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity. Reference Values:

<table>
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<th>Level</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>&lt;10.0 GPL</td>
<td>negative</td>
</tr>
<tr>
<td>10.0-14.9 GPL</td>
<td>borderline</td>
</tr>
<tr>
<td>15.0-39.9 GPL</td>
<td>weakly positive</td>
</tr>
<tr>
<td>40.0-79.9 GPL</td>
<td>positive</td>
</tr>
</tbody>
</table>

Current as of July 8, 2016 11:28 am CDT  
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Phospholipid (Cardiolipin) Antibodies, IgM, Serum

Clinical Information: The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (e.g., phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (e.g., phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2 glycoprotein 1 (beta 2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta 2 GP1. Beta 2 GP1 is a 326 amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. Only those phospholipid antibodies that are capable of cross-linking beta 2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta 2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM antiphospholipid antibody (>40 GPL, >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM anti-beta 2 GP 1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks.
Anti-cardiolipin and anti-beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.(4)

**Useful For:** Evaluation of suspected cases of antiphospholipid syndrome

**Interpretation:** APL, GPL, and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA phospholipid (cardiolipin) antibody result >15 APL with negative IgG and IgM phospholipids (cardiolipin) antibody results are not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <10.0 MPL (negative)
- 10.0-14.9 MPL (borderline)
- 15.0-39.9 MPL (weakly positive)
- 40.0-79.9 MPL (positive)
- > or =80.0 MPL (strongly positive)

MPL refers to IgM Phospholipid Units. One MPL unit is 1 microgram of IgM antibody.

Reference values apply to all ages.

**Clinical References:**

**Phospholipids, Serum**

**Clinical Information:** The phospholipids comprise about 1/3 of the total lipids in serum. These consist in a large part of a lipid, phosphatidylcholine (formerly lecithin), in which 1 of the glycerol carbons is esterified with choline phosphate. A major step in lipoprotein particle remodeling results from lecithin-cholesterol acyltransferase (LCAT) activity, which normally transesterifies free cholesterol with fatty acids derived from phosphatidylcholine. LCAT deficiency results in a lack of remodeling of primary lipoprotein particles, affecting eventual cholesterol uptake and elimination. In cases of deficiency of LCAT, the concentration of lecithin in the serum are increased several-fold. Clinical findings in LCAT deficiency include corneal opacities, anemia, and frequently, proteinuria. The disorder is inherited as an autosomal recessive trait. Early atherosclerosis develops in many individuals with this disorder. In addition, sphingomyelin normally comprises about 5% to 20% of the total phospholipids of serum. In Niemann-Pick Type A and B diseases, sphingomyelin accumulates in visceral and neural tissues and may become increased in the serum. Other disorders involving alterations of the concentration, composition, and/or lipoprotein distribution include: abeta- or hypobetalipoproteinemia, Tangier disease, or fish eye disease.

**Useful For:** First-order test in the diagnosis of lecithin-cholesterol acyltransferase deficiency

**Interpretation:** Elevated in cases of lecithin-cholesterol acyltransferase deficiency deficiency due to
Reference Values:
155-275 mg/dL

Reference values have not been established for patients who are <16 years of age.


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Phosphomannomutase (PMM) and Phosphomannose Isomerase (PMI), Fibroblasts

Clinical Information: Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of inherited metabolic diseases that affect 1 of the steps of the pathway involved in glycosylation. CDGs typically present as multisystemic disorders and may include developmental delay, hypotonia, abnormal magnetic resonance imaging (MRI) findings, hypoglycemia, and protein-losing enteropathy. There is considerable variation in the severity of this group of diseases, which can range from hydrops fetalis to a mild presentation in adults. In some subtypes (Ib, in particular) intelligence is not compromised. Phosphomannomutase-2 deficiency (CDG-Ia or PMM2-CDG) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of the enzyme phosphomannomutase-2, encoded by the PMM2 gene. Over 700 individuals have been described to date, making it the most common CDG worldwide. All patients with CDG-Ia have neurological manifestations of disease with variable involvement of other organ systems. Individuals with this disorder typically present in the neonatal period with failure to thrive, developmental delay, abnormal subcutaneous fat distribution, elevated liver transaminases, and abnormal MRI findings. Currently, there is no cure and treatment remains primarily supportive and symptomatic. Phosphomannose isomerase deficiency (CDG-Ib or MPI-CDG) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of phosphomannose isomerase, an enzyme encoded by the MPI gene. This CDG subtype is unique in that there is little to no involvement of the central nervous system. The primary clinical manifestations are a result of aberrant gastrointestinal function. In particular, individuals with CDG-Ib may present with failure to thrive, hypoglycemia, chronic diarrhea, and protein-losing enteropathy. Although CDG-Ib can be life threatening, it can be effectively treated with mannose supplementation.

Useful For: Diagnosis of congenital disorders of glycosylation Ia (phosphomannomutase-2 deficiency [CDG-Ia or PMM2-CDG]) and Ib (phosphomannose isomerase deficiency [CDG-Ib or MPI-CDG]) as measured in fibroblasts A follow-up test for patients with an abnormal transferrin isoform profile as determined by isoelectric focusing or liquid chromatography-mass spectrometry (eg, CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum)

Interpretation: Normal results are not consistent with either phosphomannomutase-2 deficiency (CDG-Ia or PMM2-CDG) or phosphomannose isomerase deficiency (CDG-Ib or MPI-CDG). Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of CDG-Ia. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of CDG-Ib. Mild to moderately reduced enzyme activities will be interpreted in the context of clinical and other laboratory test information submitted with the specimen.

Reference Values:
PHOSPHOMANNOMUTASE
Normal >700 nmol/h/mg Prot

PHOSPHOMANNOSE ISOMERASE
Normal >1,500 nmol/h/mg Prot

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PMMIF
89657

**Phosphomannomutase (PMM) and Phosphomannose Isomerase (PMI), Leukocytes**

Clinical Information: Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of inherited metabolic diseases that affect 1 of the steps of the pathway involved in glycosylation. CDGs typically present as multisystemic disorders and may include developmental delay, hypotonia, abnormal magnetic resonance imaging (MRI) findings, hypoglycemia, and protein-losing enteropathy. There is considerable variation in the severity of this group of diseases, which can range from hydrops fetalis to a mild presentation in adults. In some subtypes (Ib, in particular) intelligence is not compromised. Phosphomannomutase-2 deficiency (CDG-Ia or PMM2-CDG) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of the enzyme phosphomannomutase-2, encoded by the PMM2 gene. Over 700 individuals have been described to date, making it the most common CDG worldwide. All patients with CDG-Ia have neurological manifestations of disease with variable involvement of other organ systems. Typically, individuals with this disorder present in the neonatal period with failure to thrive, developmental delay, abnormal subcutaneous fat distribution, elevated liver transaminases, and abnormal MRI findings. Currently, there is no cure and treatment remains primarily supportive and symptomatic.

Phosphomannose isomerase deficiency (CDG-Ib or MPI-CDG) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of phosphomannose isomerase, an enzyme encoded by the MPI gene. This CDG subtype is unique in that there is little to no involvement of the central nervous system. The primary clinical manifestations are a result of aberrant gastrointestinal function. In particular, individuals with CDG-Ib may present with failure to thrive, hypoglycemia, chronic diarrhea, and protein-losing enteropathy. CDG-Ib is also unique in that it can be effectively treated with mannose supplementation, though can be fatal if left untreated.

Useful For: Diagnosis of congenital disorders of glycosylation Ia (phosphomannomutase-2 deficiency [CDG-Ia or PMM2-CDG]) and Ib (phosphomannose isomerase deficiency [CDG-Ib or MPI-CDG]) as measured in leukocytes A follow-up test for patients with an abnormal transferrin isoform profile as determined by isoelectric focusing or liquid chromatography-mass spectrometry (eg, CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum)

Interpretation: Normal results are not consistent with either phosphomannomutase-2 deficiency (CDG-Ia or PMM2-CDG) or phosphomannose isomerase deficiency (CDG-Ib or MPI-CDG). Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of CDG-Ia. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of CDG-Ib. Mild to moderately reduced enzyme activities will be interpreted in the context of clinical and other laboratory test information submitted with the specimen.

Reference Values:

**PHOSPHOMANNOMUTASE**

Normal >350 nmol/h/mg Prot

**PHOSPHOMANNOSE ISOMERASE**

Normal >1,300 nmol/h/mg Prot

Phosphorus (Inorganic), Serum

Clinical Information: Eighty-eight percent of the phosphorus contained in the body is localized in bone in the form of hydroxyapatite. The remainder is involved in intermediary carbohydrate metabolism and in physiologically important substances such as phospholipids, nucleic acids, and adenosine triphosphate (ATP). Phosphorus occurs in blood in the form of inorganic phosphate and organically bound phosphoric acid. The small amount of extracellular organic phosphorus is found exclusively in the form of phospholipids. Serum contains approximately 2.5 to 4.5 mg/dL of inorganic phosphate (the fraction measure in routine biochemical assays). Serum phosphate concentrations are dependent on meals and variation in the secretion of hormones such as parathyroid hormone (PTH) and may vary widely. Hypophosphatemia may have 4 general causes: shift of phosphate from extracellular to intracellular, renal phosphate wasting, loss from the gastrointestinal tract, and loss from intracellular stores. Hyperphosphatemia is usually secondary to an inability of the kidneys to excrete phosphate. Other factors may relate to increased intake or a shift of phosphate from the tissues into the extracellular fluid.

Useful For: Phosphate levels may be used in the diagnosis and management of a variety of disorders including bone, parathyroid and renal disease.

Interpretation: Hypophosphatemia is relatively common in hospitalized patients. Serum concentrations of phosphate between 1.5 and 2.4 mg/dL may be consider moderately decreased and are not usually associated with clinical signs and symptoms. Levels less than 1.5 mg/dL may result in muscle weakness, hemolysis of red cells, coma, and bone deformity and impaired bone growth. The most acute problem associated with rapid elevations of serum phosphate levels is hypocalcemia with tetany, seizures, and hypotension. Soft tissue calcification is also an important long-term effect of high phosphorus levels. Phosphorus levels less than 1.0 mg/dL are potentially life-threatening and are considered a critical value in the Mayo Health System.

Reference Values:
Males
- 1-4 years: 4.3-5.4 mg/dL
- 5-13 years: 3.7-5.4 mg/dL
- 14-15 years: 3.5-5.3 mg/dL
- 16-17 years: 3.1-4.7 mg/dL
- \( \geq \) or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are less than 12 months of age.

Females
- 1-7 years: 4.3-5.4 mg/dL
- 8-13 years: 4.0-5.2 mg/dL
- 14-15 years: 3.5-4.9 mg/dL
- 16-17 years: 3.1-4.7 mg/dL
- \( \geq \) or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are less than 12 months of age.


Phosphorus, 24 Hour, Urine

Clinical Information: Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption, and consequent urine excretion. Factors which increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake and proximal tubule defects (eg, Fanconi Syndrome, X-linked hypophosphatemic
Rickets, tumor-induced osteomalacia). Factors which decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients.

Useful For: Evaluation of hypo- or hyper-phosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorus excretion is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration.

Reference Values:
<1,100 mg/24 hours


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**PHBF 8029**

**Phosphorus, Body Fluid**

**Clinical Information:** Not available

**Useful For:** Not established

**Interpretation:** None available

**Reference Values:** Not applicable

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by Burtis and Ashwood. Philadelphia, WB Saunders Co, 1994

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**RPOU 84007**

**Phosphorus, Pediatric, Random, Urine**

**Clinical Information:** Approximately 80% of filter phosphorous is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorous excretion is principally dependent on regulation of proximal tubule phosphorous reabsorption. A variety of factors influence renal tubular phosphate reabsorption, and consequent urine excretion. Factors that increase urinary phosphorous excretion include high phosphorous diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake and proximal tubule defects (eg, Fanconi syndrome, X-linked hypophosphatemic rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorous excretion include low dietary phosphorous intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorous (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients.

**Useful For:** Evaluation of hypo- or hyperphosphatemic states Evaluation of patients with nephrolithiasis A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children. Therefore, this random test is offered for children <16 years old.

**Interpretation:** Interpretation of urinary phosphorous excretion is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration. Pediatric Reference Ranges on a Random Specimen Phosphate/Creatinine (mg/mg) Age (year) 5th Percentile 95th Percentile 0-1 >0.34 <5.24 1-2 >0.34 <3.95 2-3 >0.34 <3.13 3-5 >0.34 <2.17 5-7 >0.33 <1.19 7-10 >0.32 <0.97 10-14 >0.22 <0.86 14-17 >0.21 <0.75 Matos V, van Melle G, Boulat O et al: Urinary phosphatate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric
Phosphorylase Stain (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

Phthalic Anhydride, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.
Pig Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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role, including both cellular and humoral mechanisms.(1)

**Useful For:** Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to pigeon droppings

**Interpretation:** Elevated concentrations of IgG antibodies to pigeon droppings in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to this antigen.

**Reference Values:**
> or =16 years: < or =53.3 mg/L

**Clinical References:**

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**Pigeon Droppings, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.

PIGF
82145

Pigeon Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.


FPIGW
57958

Pigweed Spiny (Amaranthus spinosus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L
Pine Mix (Lodgepole, Ponderosa) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Pine Nut, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PNAP
82815

Pineapple, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.

**Pinworm Exam, Perianal**

**Clinical Information:** Enterobius vermicularis (pinworms) are nematodes (roundworms) which are found worldwide in both temperate and tropical areas. The adults reside in the upper large intestine of humans and transmission is by the fecal-oral route. Adult females migrate to the perianal area, especially during the night, and deposit large numbers of eggs. Pinworm infection is the most common helminth infection in the United States and is the most common in young school-age children of all social classes. Pinworms do not produce significant intestinal disease but can cause irritating pruritus in the perianal area. They have also been implicated in vulvovaginitis in pre-pubertal girls and possibly in urinary tract infections. Several agents are effective in treating pinworm infection (pyrantel pamoate, mebendazole), and good personal hygiene will prevent transmission of the eggs.

**Useful For:** Detection of the eggs of Enterobius vermicularis on the skin of the perianal folds

**Interpretation:** Positive results are provided indicating the presence of eggs of Enterobius vermicularis.

**Reference Values:**
Negative (reported as positive or negative)

**Clinical References:**

**Pipecolic Acid, Serum**

**Clinical Information:** Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine-dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

**Useful For:** Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Abnormal elevations of pipecolic acid can be detected in either serum or urine

**Interpretation:** Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as plasma C22-C26 very long-chain fatty acids, phytanic acid, and pristanic acid (POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum), RBC plasmalogens, and bile acid intermediates.

**Reference Values:**
<6 months: < or =6.0 nmol/mL
6 months-<1 year: < or =5.9 nmol/mL
1-17 years: < or =4.3 nmol/mL
> or =18 years: < or =7.4 nmol/mL

**Clinical References:**
Pipecolic Acid, Urine

**Clinical Information:** Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (e.g., Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

**Useful For:** Differentiating between disorders of peroxisomal biogenesis (e.g., Zellweger syndrome) and disorders with loss of a single peroxisomal function. Abnormal elevations of pipecolic acid can be detected in either serum or urine.

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**Reference Values:**
- <1 month: < or =223.8 nmol/mg creatinine
- 1-6 months: < or =123.1 nmol/mg creatinine
- 6 months-<1 year: < or =45.0 nmol/mg creatinine
- > or =1 year: < or =5.7 nmol/mg creatinine


Pistachio, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Pityrosporum orbiculare, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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PLAI
82837

Plaice, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class I or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Plasma Cell Assessment, Blood

Clinical Information: Plasma cell proliferative disorders are a group of hematologic neoplasms, all of which are derived from clonal plasma cells. These disorders exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma, a disease that most often is aggressive with poor long-term survival. Detecting plasma cell immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains) is an important element in assessing plasma cell clonality and, hence, establishing the diagnosis. Furthermore, a greater degree of peripheral blood involvement by these disorders is associated with more aggressive disease types and, therefore, is an adverse prognostic indicator. Flow cytometric immunophenotyping (FCIP) is a recognized method for detecting plasma cell Ig light chain restriction. However, shortcomings of this technique, as traditionally performed, include its relative insensitivity and its consistent underestimation of the number of clonal plasma cells present. Both of these short-comings are likely attributable to limitations of the instruments and antibodies used, as well as the presence of intraclonal phenotypic heterogeneity, which created difficulties in accurately detecting and enumerating all of the clonal plasma cells. For this reason, the FCIP plasma cell clonality assessment previously performed in our laboratory was supplemented with a slide-based immunofluorescence technique. However, recent advances in flow cytometry have led to the development of more powerful instruments and antibody reagents that allow for the use of greater antibody combinations and increased resolution of the data. With these tools, the ability of FCIP to detect and enumerate plasma cell clones has been greatly enhanced, allowing us to discontinue the supplemental, labor-intensive, slide-based plasma cell evaluation in peripheral blood specimens. The following algorithms are available in Special Instructions: -Laboratory Screening Tests for Suspected Multiple Myeloma -Laboratory Approach to the Diagnosis of Amyloidosis Also see in Publications: -Diagnosis and Monitoring of Multiple Myeloma

Useful For: Detecting peripheral blood involvement by plasma cell proliferative disorders Establishing the diagnosis of and determining prognosis for plasma cell proliferative disorders

Interpretation: In normal peripheral blood specimens, no clonal plasma cells are present (polytypic or too few to detect). Plasma cells are CD38 and CD138 positive. Normal (polyclonal, nonneoplastic) plasma cells are typically CD19-positive, whereas neoplastic (clonal) plasma cells typically are CD19-negative. CD19 expression is especially helpful in distinguishing clonal from nonclonal plasma cells when few analyzable cells are present. CD45 may be expressed by both normal and neoplastic plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population. The evaluation of these antigens aids in the identification of abnormal plasma cells, however, they will not be reported independently.

Reference Values:
CD38+/CD138+ plasma cells=0.0


Plasma Cell DNA Content and Proliferation, Bone Marrow

Clinical Information: Plasma cell proliferative disorders are a group of plasma cell derived clonal hematologic neoplasms that exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma (MM), a disease that is often aggressive with poor long-term survival. Detecting plasma cell clonality through demonstrating immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains), supplemented by the plasma cell immunophenotype and DNA index, is an important element in establishing the diagnosis. It is important to correctly classify patients with plasma cell proliferative disorders as the various disease...
entities are treated differently. A number of factors are used for this classification including the proportion clonal bone marrow plasma cells, the DNA index of the clonal plasma cells, and their proliferative activity. The plasma cell DNA index and proliferation assessment by flow cytometry are rapid and reliable. This information can be used to distinguish patients with overt active MM from less aggressive diseases such as MGUS and smoldering MM. Furthermore, in combination with other laboratory data, the results of these studies can be used as a measure of disease aggressiveness in newly diagnosed MM and also to determine therapeutic efficacy and detect disease relapse in treated MM patients. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions. Also see Diagnosis and Monitoring of Multiple Myeloma in Publications.

**Useful For:** Establishing a diagnosis of a plasma cell proliferative disorder Providing prognostic information for newly diagnosed multiple myeloma and other plasma cell proliferative disorders Assessing response to therapy and detecting disease relapse and progression in treated plasma cell proliferative disorder patients Determining plasma cell DNA content and proliferation

**Interpretation:**

Plasma Cell Clonality: Plasma cell populations with a kappa to lambda ratio of either >3.9 or <0.5 will be considered either kappa or lambda immunoglobulin light chain restricted (monotypic), respectively. As, in rare instances, immunoglobulin light chain restricted plasma cell populations may be polyclonal at the genetic level, the term monotypic rather than monoclonal plasma cells will be used. In addition to immunoglobulin light chain expression, other data collected will be used to supplement the detection of abnormal plasma cell populations. In plasma cells, CD19 expression is associated with the presence of benign, polyclonal cell populations. Therefore CD19 expression will be used as a secondary element in detecting clonal plasma cells. While loss of plasma cell CD45 expression is associated with neoplasia, CD45 is expressed by both normal and neoplastic plasma cells. Therefore, absence of plasma cell CD45 expression will be used as an aid in detecting abnormal plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population, therefore inclusion of antibodies to this antigen allows for more sensitive detection of both subtypes. In addition, as DNA content will be simultaneously assessed, the detection of plasma cell aneuploidy will also serve as a tool for identifying abnormal plasma cell populations. These additional phenotypic tools for identifying abnormal plasma cells will increase the sensitivity of the method beyond examining light chain expression; particularly in biclonal plasma cell proliferative disorders in which there are both kappa and lambda immunoglobulin light chain expressing subsets.

Plasma Cell Proliferation: The proportion of plasma cells in S-phase will be determined by measuring the proportion of cells with DNA content between the G0/G1 and G2/M peaks. In some instances, plasma cell proliferation will not be able to be determined by this method, including when there are fewer than 300 abnormal plasma cell events and when there are multiple aneuploid plasma cell populations. In newly diagnosed multiple myeloma, a plasma cell labeling index (PCLI) of > or =3.0 is associated with a more aggressive disease course.(1,2) As there was a 100% concordance between a PCLI of >3.0 and an estimated S-phase of >1.5%, and this value is published standard for identifying plasma cell neoplasms with a high proliferative rate, it will be noted in the report if the estimated S-phase exceeds this value.(3,4)

DNA Index: Processed cells are stained with DAPI to determine the DNA index of the abnormal plasma cells. This will be determined by dividing the measured DNA content of the G0/G1 abnormal plasma cells by the DNA content of the normal G0/G1 plasma cells present. For this determination, normal plasma cells are the optimal control cell population due to similarities in nuclear and overall cell size. Plasma cells with a DNA content index of <0.95 will be considered hypodiploid (worst prognosis); those with a DNA content index of >1.05 will be considered hyperdiploid (favorable prognosis). Plasma cells with a DNA index of 1.9 to 2.1 will be considered tetraploid (nonfavorable prognosis) if a confirmatory G2/M population with a DNA index of 4 is identified. As noted above, since normal plasma cells are neither hyper- nor hypodiploid, DNA index will be used as a supplemental tool in detecting clonal plasma cells. Percent Polyclonal Plasma Cells in Total Plasma Cells: It has been shown that higher percent polyclonal plasma cells in total plasma cells can mean longer progression-free survival, higher response rates, and lower frequency of high-risk cytogenetics abnormalities. Studies have also shown a higher incidence of polyploid plasma cells in monoclonal gammopathy of uncertain significance and smoldering myeloma in comparison to multiple myeloma.

**Reference Values:**

Plasma Cell Clonality:

- Normal bone marrow
- No monotypic clonal plasma cells detected
DNA Index:
Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05

cytologically and immunophenotypically identical to the plasma cell clones seen in myeloma. There are 2 primary types of plasmacytomas; solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EP). SPBs are a localized bone tumor comprised of plasma cells and account for about 5% of all plasma cell neoplasms. Common sites for SPBs are the vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula. Patients often present with pathological fracture and/or bone pain near the lesion. Treatment is typically radiation therapy; at 10 years, 35% of patients appear to be cured, 55% develop myeloma, and 10% have local recurrence. EPs are tumors of plasma cells that form in areas away from the bone and account for 3% to 5% of all plasma cell neoplasms. Approximately 80% of EPs occur in the upper respiratory tract. Less common locations include the gastrointestinal tract, bladder, testis, central nervous system, and skin. Treatment consists of radiation therapy. Regional recurrence develops in about 25% of patients, but development of myeloma is less frequent, occurring in only about 15% of patients. Genetics of both types of plasmacytomas, while not extensively studied, appears to be the same as plasma cell myeloma.

**Useful For:** Supporting the diagnosis of plasmacytoma when coordinated with a surgical pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a plasmacytoma. A negative result does not exclude the diagnosis of a plasmacytoma.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


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**PLHBB 9096**

**Plasma Hemoglobin, Plasma**

**Clinical Information:** Plasma normally contains no free hemoglobin ie, no hemoglobin that is not contained within erythrocytes. Due to normal blood draw procedures, a small amount may be present in normal people, and when detectable, the total plasma hemoglobin and the subcomponent, oxyhemoglobin, are both reported. Significant amounts of free hemoglobin occur in plasma following hemolysis for any reason. This might result from a transfusion reaction or mechanical fragmentation of red blood cells due to instrumentation, surgical procedures, or mechanical devices. Patients requiring support from extracorporeal membrane oxygenation (ECMO) or centrifugal ventricular assist devices (cVAD) are commonly monitored for trends in plasma free hemoglobin levels to assess for increasing hemolysis. Sharp spikes in plasma hemoglobin levels can indicate pump disruption. However, plasma hemoglobin can be artifactually increased due to a traumatic blood draw or prolonged exposure to post-draw red blood cells. Additionally, bilirubin interferes substantially with the ability to calculate total plasma hemoglobin levels and gives spurious and unreliable results, a difficulty frequently encountered in serially tested patients. When this occurs, the oxyhemoglobin level tends to show less interference and it is the only analyte reported in the presence of increased bilirubin (>5 mg/dL). When using trending data, total plasma hemoglobin and oxyhemoglobin levels are not interchangeable and should be compared within their subgroups only.

**Useful For:** Determining whether hemolysis is occurring such as from: -Transfusion reaction -Mechanical fragmentation of red blood cells -Relative comparison to baseline levels in extracorporeal membrane oxygenation (ECMO) and centrifugal ventricular assist device (cVAD) patients to assess pump disruption

**Interpretation:** Total hemoglobin: > or =12 months: 0.0-15.2 mg/dL Reference values have not been established for patients who are <12 months of age. Oxyhemoglobin: > or =12 months: 0.0-12.4 mg/dL Reference values have not been established for patients who are <12 months of age.

**Reference Values:**
TOTAL HEMOGLOBIN
> or =12 months: 0.0-15.2 mg/dL
Reference values have not been established for patients who are <12 months of age.

OXYHEMOGLOBIN
> or =12 months: 0.0-12.4 mg/dL
Reference values have not been established for patients who are <12 months of age.


Plasminogen Activator Inhibitor Antigen, Plasma

Clinical Information: Plasminogen activator inhibitor type 1 (PAI-1) antigen is a single-chain glycoprotein (MW 50,000) produced by endothelial cells and hepatocytes and is also present in alpha granules of platelets. PAI-1 is a serine protein inhibitor that is secreted in response to inflammatory reactions. Platelet alpha granules contain large amounts of PAI-1, which is released during vascular injury and assists in fibrin clot stability. PAI-1 is synthesized in the active form but has marked functional instability and a functional half-life of about 2 hours in vivo. Circulating PAI-1 is bound to vitronectin, which protects the inhibitor from inactivation and may assist in targeting the inhibitor to sites of vascular injury. At least 4 different conformations of PAI-1 have been described: 1) the active form that reacts with plasminogen activator; 2) a latent form that is nonreactive; 3) a substrate form that can be cleaved by plasminogen activators but is noninhibitory; and 4) the inert form of PAI-1 generated by the cleavage of the reactive site. PAI-1 is the main inhibitor of tissue-type plasminogen activator (tPA) and urokinase plasminogen activator (uPA) and, as such, plays an important role in the regulation of fibrinolysis. Elevated levels of PAI-1 result in deficient plasminogen activation and are associated with a predisposition to thrombosis, including veno-occlusive disease (VOD) after bone marrow transplantation (BMT). Primary injury to the hepatic sinusoidal endothelium and hepatocytes induced by high-dose chemoradiotherapy is believed to be the key event in the pathogenesis of VOD. The clinical diagnosis of VOD is complex because the clinical signs and symptoms can occur as a result of other processes that can complicate the posttransplant period such as sepsis, graft-versus-host disease (GVHD), cyclosporine toxicity, other medications, hemolysis, or parenteral nutrition. Liver biopsy, although safer since the widespread introduction of transjugular procedures, remains hazardous in this thrombocytopenic population. A sensitive and specific assay would be invaluable in guiding management and avoiding potentially hazardous invasive diagnostic procedures. Along these lines several investigators have studied various markers of hypercoagulability for possible pathogenic and predictive relevance. Aside from serum bilirubin level, no laboratory marker has been standardized as a diagnostic marker of VOD and the severity of VOD remains retrospectively defined. Lee et al analyzed 115 patients after allogenic BMT in an attempt to identify diagnostic and severity markers of VOD. Of the 115 patients, 50 developed VOD.(1) Multiple logistic regression models were constructed that included recognized relevant clinical and hemostatic variables. Of the hemostatic variables, only PAI-1 antigen was identified as an independent marker for the occurrence of VOD. This confirmed findings of an earlier, smaller study, that PAI-1 is a powerful diagnostic marker of VOD during the early period post-BMT, and can distinguish VOD from other causes of hyperbilirubinemia post-BMT such as GVHD and drug toxicity. Furthermore, PAI-1 antigen and bilirubin were independent variables for predicting severe VOD. Familial thrombosis has been associated with inherited elevation of plasma PAI-1 activity. Increased levels of PAI-1 have also been reported in a number of conditions including malignancy, liver disease, the postoperative period, septic shock, the second and third trimesters of pregnancy, obesity, and coronary heart disease. Low plasma levels of the active form of PAI-1 have been associated with abnormal, clinically significant bleeding. Complete deficiency of PAI-1, either congenital or acquired, is associated with bleeding manifestations that include hemarthroses, hematomas, menorrhagia, easy bruising, and postoperative
hemorrhage.

**Useful For:** Identification of heredity elevation or deficiency of plasminogen activator inhibitor type 1
Determination of risk for veno-occlusive disease associated with bone marrow transplantation
Differential diagnosis of impaired fibrinolysis
Prognostic marker of occurrence or recurrence of thrombosis

**Interpretation:** Increased levels of plasminogen activator inhibitor type 1 (PAI-1) are associated with
a predisposition to thrombosis. Decreased or absent levels of detectable functional PAI-1 will result in a
life-long bleeding diathesis.

**Reference Values:**
3-72 ng/mL

**Clinical References:**
1. Lee JH, Lee KH, Lee JH, et al: Plasminogen activator inhibitor-1 is an
independent diagnostic marker as well as severity predictor of hepatic veno-occlusive disease after
allogeneic bone marrow transplantation in adults conditioned with busulphan and cyclophosphamide. Br J
Haematol 2002;118:1087-1094
Hemostasis and Thrombosis. Edited by RW Colman, J Hirsh, VJ Marder, et al. Philadelphia, Lippincott,
2001, pp 355-365
3. Vaughn DE, Declerck PJ: Regulation of fibrinolysis. In Thrombosis and
5. Kruthof EK, Gudinchet A, Bachman F: Plasminogen activator inhibitor-1 and plasminogen activator inhibitor-2 in various
inhibitor-1 confirms the diagnosis of hepatic veno-occlusive disease in patients with hyperbilirubinemia
after bone marrow transplantation. Blood 1997;89:2184-2188

**FPACT**
91760
**Plasminogen Activator Inhibitor-1, 4G/5G Genotyping (PAI-1) Polymorphism**

**Reference Values:**
A final report will be attached in MayoAccess.

**PSGN**
9079
**Plasminogen Activity, Plasma**

**Clinical Information:** During the formation of a hemostatic (fibrin) plug, biochemical mechanisms
are initiated to limit the extent of the hemostatic process at the site of injury and maintain vascular
patency. This process of fibrinolysis is defined as the plasmin-mediated degradation of fibrin. Plasmin
limits the extent of the hemostatic process at the site of vessel injury. Plasmin is generated from its
precursor, plasminogen, by plasminogen activators (ie, tissue plasminogen-activator [tPA], urokinase-type
plasminogen activator [uPA]). Plasminogen is a single-chain glycoprotein that is synthesized in the liver
and has a biologic half-life of approximately 2 days.(1) Deficiency of plasminogen may be inherited or
acquired. Persons with congenital plasminogen deficiency may have an increased risk for thrombosis.
Homozygous deficiency has been associated with thromboembolic disease and ligneous conjunctivitis.
The risk of thrombosis for heterozygous plasminogen deficiency is uncertain. This risk likely is
compounded when combined with other inherited or acquired thrombophilias. Congenital deficiency of
plasminogen is autosomally transmitted and rare, both in the general population and thrombosis patients,
with a prevalence of approximately 0.4% and 1% to 3%, respectively.(2) Based on the results of
functional and immunologic (antigenic) assays, 2 types of plasminogen deficiency have been identified:
-Quantitative deficiency (type I)-defined by a corresponding decrease in both plasminogen activity and
antigen level -Functional deficiency (type II)-caused by a normally synthesized but dysfunctional
plasminogen This plasminogen activity assay will identify both types of deficiency. Acquired causes of
plasminogen deficiency include consumption such as with thrombolytic therapy (urokinase, tPA) or
disseminated intravascular coagulation and fibrinolysis (DIC/ICF), or decreased synthesis (liver
**Useful For:** Evaluating patients with incident or recurrent thromboembolic events Evaluating individuals with a family history of thrombophilia (venous or arterial) Evaluating patients with ligneous conjunctivitis (strong association with homozygous plasminogen deficiency) Evaluating fibrinolysis, in combination with other components of the fibrinolytic system (fibrinogen, tPA-inhibitor, and d-dimers)

**Interpretation:** Plasminogen activity <75% may represent a congenital deficiency state, if acquired deficiency can be excluded. Hereditary abnormalities of plasminogen (deficiency or dysfunction) are very uncommon. Acquired causes of plasminogen deficiency are much more common and may be the result of consumption due to thrombolytic therapy or intravascular coagulation and fibrinolysis or decreased synthesis (ie, liver disease). Plasminogen levels are low at birth (approximately 50% of adult normal level) and reach adult levels at 6 months of age.

**Reference Values:**
75-140%


**Platelet Antibodies, Indirect (IgG, IgM, IgA)**

**Interpretation:** Circulating antibodies to platelets, detected by Flow Cytometry, are found in the sera of patients with immune mediated disorders. Platelet antibodies have been associated with ITP and drug-induced thrombocytopenia.

**Reference Values:**
Negative

**Platelet Antibody, Serum**

**Clinical Information:** Platelet antibodies may be allo- or autoantibodies and may be directed to a wide range of antigenic "targets" carried on platelet cytoplasmic membranes. Platelet alloantibodies are involved in several clinical situations such as alloimmune platelet refractoriness (APR), neonatal alloimmune thrombocytopenic purpura (NATP), and posttransfusion purpura (PTP). In these settings, the antibodies, usually HLA Class I in the case of APR, and platelet-specific antibodies eg, HPA-1a (PLA1) in the case of NATP or PTP, are found in the patient's plasma and are detected by tests performed on serum. In contrast, conditions such as idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), or sepsis are associated with the presence of excessive platelet associated immunoglobulin usually IgG. Testing for cell bound platelet antibody is indicated for the diagnosis of these autoimmune conditions. In some cases of ITP, platelet antibodies can also be found in the patient's serum but with less frequently than cell bound antibody.

**Useful For:** Evaluating cases of immune platelet refractoriness, posttransfusion purpura, or neonatal alloimmune thrombocytopenic purpura

**Interpretation:** Presence of reactivity to some glycoproteins has no clearly established clinical significance. Results are based on clinical situation as well as test results. Serum platelet antibody testing by solid-phase enzyme-linked immunoassay offers more than a positive/negative result. When the patient's serum is positive, the specific platelet glycoprotein will be identified as well as the probable specificity. The platelet glycoproteins reported are: IIb/IIIa, Ia/IIa, GPIb/IX. Specificities include the following: HPA-1a (PL[a1]), HPA-1b (PL[a2]), HPA-3a (BAK[a]/LEK[a]), HPA-3b (BAK[b]), HPA-5b (Br[a]), HPA-5a (Br[b]). Those specificities listed in parenthesis refer to old nomenclature. In addition, this assay screens for HLA Class I antibodies, but specificity is not determined.
Platelet Surface Glycoprotein by Flow Cytometry, Blood

**Clinical Information:** Platelets have essential roles in primary hemostasis. Exposed collagen at a vascular damage site can activate platelets via collagen receptor GPVI and GPIa and bind shear-stretched multimeric VWF proteins, which subsequently interact with the platelet surface receptor, GPIb-V-IX. Upon full activation, platelets can aggregate by binding to fibrinogen through activated GPIIb-GPIIIa receptors. Deficiency of platelet surface glycoproteins can cause bleeding diathesis. Platelet flow cytometric analysis is the preferred method to assess hereditary platelet disorders due to quantitative surface glycoprotein (GP) deficiencies. GP expression levels can be measured by using fluorescent-conjugated GP-specific antibodies and their fluorescent intensities can be compared to normal ranges of various glycoproteins.

**Useful For:** Identification of markedly decreased CD41 (GPIIb) and CD61 (GPIIIa) expression levels, which are diagnostic for Glanzmann thrombasthenia Identification of markedly decreased CD42a (GPIX) and CD42b (GPIb-alpha) expression levels, which are diagnostic for Bernard-Soulier syndrome Identification of decreased GPVI expression, which suggests collagen receptor deficiency Identification of decreased CD49b (GPIa), which suggests collagen receptor deficiency

**Interpretation:** CD Markers % Reference Range Median Comments CD41 and CD61 50%-69% (Marginally) Marginally decreased platelet surface receptors CD41 (GPIIb) and CD61 (GPIIIa) are of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, benign polymorphisms, or a heterozygous state of Glanzmann thromboasthenia. Recommend correlation with patientâ€™s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50%: (Moderately) <30%: (Markedly) Platelet surface expression of CD41 (GPIIb) and CD61 (GPIIIa) are moderately (markedly) decreased. This finding is suggestive for a variant of Glanzmann thromboasthenia. Recommend correlation with patientâ€™s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. CD42a and CD42b 50%-69% (Marginally) Marginally decreased platelet surface receptors CD42a (GPIX) and CD42b (GPIb-alpha) are of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, benign polymorphisms, or a heterozygous state of Bernard-Soulier syndrome. Recommend correlation with patientâ€™s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50%: (Moderately) <30%: (Markedly) Platelet surface expression of CD42a (GPIX) and CD42b (GPIb-alpha) are moderately (markedly) decreased. This finding is suggestive for a variant of Bernard-Soulier syndrome. Recommend correlation with patientâ€™s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. CD49b 30%-59% (Marginally) Marginally decreased platelet surface receptor CD49b (GPIa) is of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, a benign polymorphism, or a variant of platelet collagen receptor glycoprotein Ia/IIa deficiency. Recommend correlation with patientâ€™s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 10%-30% (moderately) <10% (Markedly) Platelet surface expression of CD49b (GPIa) is moderately (markedly) decreased. This finding is suggestive for a variant of a variant of platelet collagen receptor glycoprotein Ia/IIa deficiency. Recommend correlation with patientâ€™s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if...
clinically indicated. GPVI 50%-69% (Marginally) Marginally decreased platelet surface receptor glycoprotein VI (GPVI) is of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, a benign polymorphism or a variant of platelet collagen receptor GPVI deficiency. Recommend correlation with patient’s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50% (moderately) <30% (Markedly) Platelet surface expression of glycoprotein VI (GPVI) is moderately (markedly) decreased. This finding is suggestive for a variant of a variant of platelet collagen receptor GPVI deficiency. Recommend correlation with patient’s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated.

Reference Values:

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<th>Name</th>
<th>Normal Range (Median)</th>
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<tr>
<td>GPIIb CD41</td>
<td>&gt;70.0%</td>
</tr>
<tr>
<td>GPIIIa CD61</td>
<td>&gt;70.0%</td>
</tr>
<tr>
<td>GPX CD42a</td>
<td>&gt;70.0%</td>
</tr>
<tr>
<td>GPIb-alpha CD42b</td>
<td>&gt;70.0%</td>
</tr>
<tr>
<td>GP la CD49b</td>
<td>&gt;60.0%</td>
</tr>
<tr>
<td>GPVI</td>
<td>&gt;70.0%</td>
</tr>
</tbody>
</table>

Clinical References:

Platelet Transmission Electron Microscopic Study

Clinical Information: Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life threatening. A reliable laboratory diagnosis of a platelet disorder can significantly impact patients and, potentially, their family members' clinical management and outcome. Platelet transmission electron microscopy (PTEM) has been an essential tool for laboratory diagnosis of various hereditary platelet disorders since it was first used to visualize fibrin-platelet clot formation in 1955. PTEM employs 2 main methods to visualize platelet ultrastructure, whole mount (WM) TEM and thin section (TS) TEM. WM-TEM is considered the gold standard test for diagnosing dense granule deficiencies in Hermansky-Pudlik syndrome, alpha-delta platelet storage pool deficiency, Paris-Trousseau-Jacobsen syndrome, Wiskott-Aldrich syndrome, TAR (thrombocytopenia, absent radii) syndrome, Chediak-Higashi syndrome, and more. TS-TEM is a preferred method to visualize platelet alpha granules, other organelles and abnormal inclusions. Platelet disorders that can be detected by PTEM include (but are not limited to): Delta granules (dense bodies): -Hermansky Pudlik syndrome -Wiskott-Aldrich syndrome -Chediak Higashi syndrome -Jacobson/Paris Trousseau syndrome -York platelet syndrome -Storage pool deficiency, not otherwise specified Alpha granules: -Gray platelet syndrome -White platelet syndrome -X-linked GATA 1 mutation -Jacobson/Paris Trousseau syndrome Alpha and delta granules: -Alpha-delta storage pool deficiency

Useful For: Diagnosing platelet disorders

Interpretation: Ultrastructural abnormalities identified by platelet transmission electron microscopy are evaluated by a Mayo hematopathologist. Platelet size, alpha granules, golgi complex, and abnormal
inclusions will be assessed as part of the morphologic examination under transmission electron microscopy. Distinct and sometimes pathognomonic ultrastructural abnormalities are found in Hermansky Pudlak syndrome, gray platelet syndrome with virtually absent alpha granules, white platelet syndrome, Medich giant platelet disorder, X-linked GATA-1 macrothrombocytopenia, and, recently described, York platelet syndrome.

**Reference Values:**

Mean dense granules/platelet ≥ 1.2

**Clinical References:**


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**Platinum, Serum**

**Clinical Information:** Cisplatin (cis-diaminedichloroplatinum)(1) and carboplatin (cyclobutanedicarboxylatoplatinum)(2,3) are used in cancer chemotherapy. Clinical trials demonstrate schedule-dependent activity of carboplatin in patients with relapsed and refractory acute leukemia. Patients responding to carboplatin therapy had peak serum platinum concentration in the range of 0.6 to 1.8 mcg/mL. Trough concentrations ranged from 0.1 to 0.4 mcg/mL. Platinum concentrations maintained >1.8 mcg/mL can induce neutropenia and renal failure if coadministered with nephrotoxic antibiotics.(1,2) Unexposed individuals should have platinum concentrations <0.04 mcg/mL.(4)

**Useful For:** Monitoring platinum levels in patients receiving cisplatin or other platinum-containing drugs

**Interpretation:** Effective Range: -Patients responding to carboplatin therapy had peak plasma platinum concentration in the range of 0.6 to 1.8 mcg/mL. -Trough concentrations range from 0.1 to 0.4 mcg/mL. -Platinum concentrations maintained >1.8 mcg/mL can induce neutropenia, and renal failure if coadministered with nephrotoxic antibiotics. -Unexposed patients should have platinum concentrations <0.04 mcg/mL.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
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<tbody>
<tr>
<td>Cisplatin Infusion, Peak</td>
<td>0.6-1.8 mcg/mL</td>
</tr>
<tr>
<td>Cisplatin Infusion, Trough</td>
<td>0.1-0.4 mcg/mL</td>
</tr>
<tr>
<td>Unexposed</td>
<td>&lt;0.04 mcg/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**


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**Plum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
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<td>0.35-0.69</td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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</tbody>
</table>


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**PML/RARA Quantitative, PCR**

**Clinical Information:** Acute promyelocytic leukemia (APL) accounts for 5% to 10% of acute myeloid leukemia, and generally has a good prognosis with current treatment protocols. APL cells contain a fusion gene comprised of the downstream sequences of the retinoic acid receptor alpha gene (RARA) fused to the promoter region and upstream sequences of one of several genes, the most common (>80%) being the promyelocytic leukemia gene (PML). The fusion gene is designated PML/RARA and may be seen in a karyotype as t(15;17)(q22;q12). Messenger RNA (PML/RARA) produced from the fusion gene can be detected using a PCR-based assay, and indicates the presence of neoplastic cells. The PCR-based assay has greater sensitivity than standard methods such as morphology review, karyotyping, or FISH. Recent studies have indicated that sensitive monitoring is important because the majority of patients who remain PCR positive, or become PCR positive again following treatment, will relapse and likely benefit from early intervention for residual/recurrent disease. This quantitative assay allows PML/RARA levels to be monitored rather than simply detecting the presence or absence of disease.

**Useful For:** Diagnosis of acute promyelocytic leukemia (APL) Detection of residual or recurrent APL Monitoring the level of promyelocytic leukemia/retinoic acid receptor alpha (PML/RARA) in APL patients

**Interpretation:** The assay is reported in the form of a normalized ratio of promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) fusion transcript to the control gene GusB expressed as a percentage, which is an estimate of the level of PML/RARA RNA present in the specimen, expressed in relation to the level of RNA from an internal control gene (beta glucuronidase, designated GUSB). The normalized ratio has no units but is directly related to the level of PML/RARA detected (ie, larger numbers indicate higher levels of PML/RARA and smaller numbers indicate lower levels). A relative expression value minimizes variability in the RNA levels measured in separate specimens tested at different times. Although a quantitative PCR assay is performed, the precision of the assay is such that
results must be considered semiquantitative, and it is recommended that only log changes be considered significant. Critical results, such as a change in the status of positivity, should be repeated on a separate specimen to verify the result.

**Reference Values:**
An interpretive report will be provided.

If positive, a value representing a ratio of PML-RARA fusion transcript to the control gene GusB expressed as a percentage will be reported.

promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes, and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, café au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability and/or immunohistochemistry for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of PMS2 are more likely to have a germline mutation in the PMS2 gene.

**Useful For:** Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer
Determining whether absence of PMS2 protein in tumor tissue, as demonstrated by immunohistochemistry, is associated with a germline mutation in the affected individual Identification of familial PMS2 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
PNRP 81698

**Pneumocystis jiroveci, Molecular Detection, PCR**

**Clinical Information:** Pneumocystis pneumonia is an important cause of opportunistic infection in immunocompromised patients, particularly those with HIV. The causative agent, Pneumocystis jiroveci, cannot be cultured in vitro and, therefore, laboratory detection has historically relied upon microscopic identification directly from patient specimens using fluorescent stains or antibodies. Unfortunately, stains often lack sensitivity and require expertise on the part of the reader in order to differentiate Pneumocystis jiroveci from staining artifacts and other fungi. This real-time PCR assay provides sensitive (21% more sensitive than direct detection using fluorescent calcofluor white stain), specific, and objective detection of Pneumocystis from bronchoalveolar lavage fluid and other specimens.

**Useful For:** Preferred test for detection of Pneumocystis

**Interpretation:** A positive result indicates the presence of Pneumocystis DNA. A negative result indicates the absence of detectable Pneumocystis DNA.

**Reference Values:** Not applicable

**Clinical References:**

FPJD 58046

**Pneumocystis jirovecii DFA**

**Reference Values:**
Negative

SPN 8047

**Pneumocystis Smear**

**Clinical Information:** Pneumocystis jiroveci is one of the major microbial pathogens associated with opportunistic pulmonary infections in patients receiving immunosuppressive therapy or with immune deficiencies. Presently, the most common means to diagnose Pneumocystis jiroveci infection is by microscopic detection of the organisms in specimens such as bronchoalveolar lavage, open lung biopsy tissue, induced sputum and transtracheal aspirate.

**Useful For:** Diagnosis of Pneumocystis jiroveci pneumonia

**Interpretation:** Negative: no cysts observed Positive: cysts present

**Reference Values:**
Negative

PNH, PI-Linked Antigen, Blood

Clinical Information: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disorder characterized by nocturnal hemoglobinuria, chronic hemolytic anemia, thrombosis, pancytopenia, and, in some patients, acute or chronic myeloid malignancies. PNH appears to be a hematopoietic stem cell disorder that affects erythroid, granulocytic, and megakaryocytic cell lines. The abnormal cells in PNH have been shown to lack glycosylphosphatidylinositol (GPI)-linked proteins in erythroid, granulocytic, megakaryocytic, and, in some instances, lymphoid cells. Mutations in the phosphatidylinositol glycan A gene, PIGA, have been identified consistently in patients with PNH, thus confirming the biological defect in this disorder. A flow cytometric-based assay can detect the presence or absence of these GPI-linked proteins in granulocytes, monocytes, erythrocytes, and/or lymphocytes, thus avoiding the problems associated with red cell-based diagnostic methods (Ham's test) in which recent hemolytic episodes or recent transfusions can give false-negative results. A partial list of known GPI-linked proteins include CD14, CD16, CD24, CD55, CD56, CD58, CD59, C8-binding protein, alkaline phosphatase, acetylcholine esterase, and a variety of high frequency human blood antigens. In addition, fluorescent aerolysin (FLAER) binds directly to the GPI anchor and can be used to evaluate the expression of the GPI linkage. Our studies, as well as others in the literature, have shown that flow cytometry-based assays will detect all Ham's-positive PNH cases, as well as some Ham's-negative PNH cases. This assay replaces the sugar water test and the Ham's test for the evaluation of patients with possible PNH. Patients with PNH should be transfused with ABO-specific RBCs, which do not need to be washed. If, for some reason, they need to receive non-ABO type-specific (type O) cells, these RBC units should be washed. Since recipient antibodies to granulocyte antigens can trigger hemolytic episodes in PNH, these patients should receive leukoreduced RBCs and platelets if they have such antibodies.

Useful For: Screening for and confirming the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) Monitoring patients with PNH

Interpretation: Individuals with paroxysmal nocturnal hemoglobinuria (PNH) have absent or decreased expression of all the glycosylphosphatidylinositol (GPI)-linked antigens and fluorescent aerolysin (FLAER) on peripheral blood cells derived from the PNH clone. Recent data showed that small PNH clones can be detected in a relatively high percentage of cases of aplastic anemia and myelodysplastic syndrome. While the significance of this finding is still uncertain, it appears that these patients may benefit from immunosuppressive therapy. This test incorporates a sophisticated technique of separating different cell populations using gating on antigen-positive cells, as well as the sensitivity to enable detection of small PNH clones. In addition, this test detects a partial loss of CD59 on RBCs (type II RBC). Patients with large proportion of type II RBC are unlikely to show high levels of hemolysis, unlike patients with complete loss of GPI-linked proteins (predominantly type III cells). While PNH is a disorder of hematopoietic stem cells and all lineages are affected, the percentage of affected cells can differ between lineages, most commonly due to RBC hemolysis and/or transfusion. Individuals without PNH have normal expression of FLAER (neutrophils and monocytes) and normal expression of all GPI-linked antigens-CD14 (monocytes), CD16 (neutrophils and NK cells), CD24 (neutrophils), and CD59 (RBCs).

Reference Values:
An interpretive report will be provided.

RED BLOOD CELLS:
PNH RBC-Partial Antigen loss: 0.00-0.99%
PNH RBC-Complete Antigen loss: 0.00-0.01%
PNH Granulocytes: 0.00-0.01%
PNH Monocytes: 0.00-0.05%

**Clinical References:**

**FPOLO**

**Poliovirus (Types 1, 3) Antibodies, Neutralization**

**Reference Values:**
Polio 1 Titer: <1:8
Polio 3 Titer: <1:8

The presence of neutralizing serum antibodies (titers 1:8 up to >1:128) against polioviruses implies lifelong immunity. Some persons without detectable titers (<1:8) may also be immune as demonstrated by elicitation of a secondary-type serum antibody response upon rechallenge with live polio vaccine.

**FPOLE**

**Pollock White (Pollachius virens) IgE**

**Interpretation:**
Class IgE (kU/L) Comment
0 0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline
1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive
3 3.50 - 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive
5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**TALDO**

**Polyols, Quantitative, Urine**

**Clinical Information:** Polyols are sugar alcohols that have been identified in blood, urine, and cerebrospinal fluid. Characteristic patterns of abnormal polyols may suggest a disorder of the pentose phosphate pathway (PPP) including transaldolase (TALDO) deficiency and ribose-5-phosphate isomerase (RPI) deficiency. The PPP is involved in carbohydrate metabolism and is present in the cytosol of all cells. Two specific functions of the PPP are the production of nicotinamide adenine dinucleotide phosphate (NADPH) and the synthesis of ribose-5-phosphate, a molecule necessary for nucleotide and nucleic acid synthesis. Both TALDO and RPI deficiency that have multisystem involvement are recently described disorders of this pathway. TALDO deficiency is an autosomal recessive disorder caused by a reduction in the enzyme transaldolase. Clinical manifestations are characterized by severe neonatal liver
failure, coagulopathy, low serum protein, hypoglycemia, high ammonia, progressive myocardial hypertrophy, and abnormal lactate dehydrogenase with remarkably normal or low transaminases. Patients may present in the antenatal period with maternal HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), hydrops fetalis and oligohydramnios, dysmorphic features, cutis laxa, and hypertrichosis. The clinical course is variable, but acute liver failure with normal transaminases is a common finding. Initially, hepatomegaly is absent, but the spleen may be enlarged. Later, hepatomegaly with liver cirrhosis and mild kidney failure occur. RPI deficiency is an autosomal recessive disorder caused by a deficiency of the enzyme ribose-5-phosphate isomerase. Clinical manifestations include neurological deficits such as slow progressing leukoencephalopathy and neuropathy. Additionally, spasticity, ataxia, epilepsy, regression, and delayed psychomotor development have been described. Polyols analysis in urine is the method of choice for the biochemical diagnosis of TALDO and RPI deficiency. Abnormal results should be followed with either enzymatic or molecular genetic analysis.

**Useful For:** Diagnosis of transaldolase (TALDO) deficiency or ribose-5-phosphate isomerase (RPI) deficiency

**Interpretation:** An interpretive report is provided. All profiles are reviewed by the laboratory director and interpretation is based on pattern recognition. A detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 months</td>
<td>1-3 years</td>
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<tr>
<td>Erythritol</td>
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<td>Arabinitol</td>
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<tr>
<td>Ribitol</td>
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<tr>
<td>Sedoheptulose</td>
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</tr>
</tbody>
</table>

Values are expressed in mmol/mol creatinine

**Clinical References:**

**FPOM 57918**

**Pomegranate (Punica granatum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FPOPW 57557**

**Poplar White (Populus alba) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**POPSD 82632 Poppy Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>6</td>
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<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**FPORG 57627 Pork IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility
of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Pork IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**

<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**Pork Neutral-Regular Insulin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Pork, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase. Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with deficiency mutation in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of porphobilinogen deaminase (PBGD) enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (HMBSS / HMBS Gene, Full Gene Analysis) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

**Useful For:** Confirmation of a diagnosis of acute intermittent porphyria (AIP)

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
Reference ranges have not been established for patients who are <16 years of age.

- > or =7.0 nmol/L/sec
- 6.0-6.9 nmol/L/sec (indeterminate)
- <6.0 nmol/L/sec (diminished)

**Clinical References:**

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**Porphobilinogen Deaminase (PBGD), Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase. Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with deficiency mutation in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode.
episode. In addition, the diagnosis of AIP can be confirmed through the measurement of porphobilinogen deaminase (PBGD) enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (HMBSZ / HMBS Gene, Full Gene Analysis) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

Useful For: Confirmation of a diagnosis of acute intermittent porphyria (AIP)

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
Reference ranges have not been established for patients who are <16 years of age.

- > or =7.0 nmol/L/sec
- 6.0-6.9 nmol/L/sec (indeterminate)
- <6.0 nmol/L/sec (diminished)

Clinical References:

Porphyrobilinogen, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Urinary porphobilinogen (PBG) is elevated during the acute phase of the neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to distinguish between AIP, HCP and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity (PBGD / Porphobilinogen Deaminase [PBGD], Whole Blood). VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces). Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available for AIP (HMBSZ / HMBS Gene, Full Gene Analysis), HCP (CPOXZ / CPOX Gene, Full Gene Analysis), or VP (PPOXZ / PPOX Gene, Full Gene Analysis) which allows for diagnosis of at-risk family members. The work up of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

Useful For: First-line test for evaluation of a suspected acute porphyria: acute intermittent porphyria,
hereditary coproporphyria, and variegate porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
< or =1.3 mcmol/L

**Clinical References:**

**PEWE 31893**

**Porphyrins Evaluation, Washed Erythrocytes**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by diminished ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fraction is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and free protoporphyrin are necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase -Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies. There are 2 test options: PEE / Porphyrins Evaluation, Whole Blood and PEWE / Porphyrins Evaluation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Preferred test for analysis of erythrocyte porphyrins Establishing a biochemical diagnosis of erythropoietic protoporphyria, and X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with
the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:**

**PORPHYRINS, TOTAL, RBC**

<80 mcg/dL packed cells

**FREE PROTOPORPHYRIN**

<20 mcg/dL packed cells

**ZINC-COMPLEXED PROTOPORPHYRIN**

<60 mcg/dL packed cells

**Clinical References:**


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**Porphyrias Evaluation, Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by diminished ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fraction is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and noncomplexed (free) protoporphyrin is necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies. There are 2 test options: PEE / Porphyrs Evaluation, Whole Blood and PEWE / Porphyrs Evaluation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes,
which are stable for 14 days, should be submitted.

**Useful For:** Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:**

- **PORPHYRINS, TOTAL, RBC**
  - <80 mcg/dL packed cells

- **FREE PROTOPORPHYRIN**
  - <20 mcg/dL packed cells

- **ZINC-COMPLEXED PROTOPORPHYRIN**
  - <60 mcg/dL packed cells

**Clinical References:**


**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms, which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfon drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly sporadic (acquired), but in about 25% of cases it is inherited in...
an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) occurs when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Increased fecal porphyrin excretions are observed most commonly in symptomatic patients with CEP, PCT, HCP, and VP. In quiescent phases, as well as prior to puberty, fecal porphyrin excretion may be within normal limits. Patients with AIP may have elevated fecal porphyrin levels during severe attacks. EPP and XLDPP patients may have elevated protoporphyrin levels, however, these disorders cannot be diagnosed by fecal analysis alone. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

**Useful For:** Evaluation of patients who present with signs or symptoms suggestive of porphyria cutanea tarda, hereditary coproporphyria, variegate porphyria, congenital erythropoietic porphyria, erythropoietic protoporphyria, or X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
- **UROPORPHYRIN I**
  - <120 mcg/24 hours
- **UROPORPHYRIN III**
  - <50 mcg/24 hours
- **HEPTACARBOXYL PORPHYRIN I**
  - <40 mcg/24 hours
- **HEPTACARBOXYL PORPHYRIN III**
  - <40 mcg/24 hours
- **ISOHEPTACARBOXYL PORPHYRINS**
  - <30 mcg/24 hours
- **HEXACARBOXYL PORPHYRIN I**
  - <10 mcg/24 hours
- **HEXACARBOXYL PORPHYRIN III**
  - <10 mcg/24 hours
- **ISOHEXACARBOXYL PORPHYRINS**
  - <10 mcg/24 hours
- **PENTACARBOXYL PORPHYRIN I**
  - <20 mcg/24 hours
PENTACARBOXYL PORPHYRIN III
<20 mcg/24 hours

ISOPENTACARBOXYL PORPHYRINS
<80 mcg/24 hours

COPROPORPHYRIN I
<500 mcg/24 hours

COPROPORPHYRIN III
<400 mcg/24 hours

ISOCOPROPORPHYRIN
<200 mcg/24 hours

PROTOPORPHYRINS
<1,500 mcg/24 hours

COPROPORPHYRIN III/COPROPORPHYRIN I RATIO
<1:20

See The Heme Biosynthetic Pathway in Special Instructions.

an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatooerythropoietic porphyria (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Urinary porphyrin determination is helpful in the diagnosis of most porphyrias including CEP, PCT, AIP, HCP, and VP. In addition, measurement of porphobilinogen (PBG) in urine is important in establishing the diagnosis of the acute neurologic porphyrias (AIP, HCP and VP). Neither urine porphyrins nor PBG is helpful in evaluating patients suspected of having EPP or XLDPP. In addition, porphyrinuria may result from exposure to certain drugs or toxins or other medical conditions (i.e., hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of uroporphyrin and/or coproporphyrin in urine. The work up of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

**Useful For:** Preferred screening test during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria (additional confirmatory testing is required to establish a diagnosis) when specimen transport will be longer than 72 hours. If the specimen will be received at Mayo Medical Laboratories within 72 hours of collection, PQNRU / Porphyrins, Quantitative, Random, Urine is recommended. Preferred screening test to begin assessment for congenital erythropoietic porphyria and porphyria cutanea tarda (additional confirmatory testing is required to establish a diagnosis)

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

UROPOPHRYRINS (octacarboxyl)

< or =30 nmol/24 hours

HEPTACARBOXYLPORPHYRINS

< or =9 nmol/24 hours

HEXACARBOXYLPORPHYRINS

< or =8 nmol/24 hours

PENTACARBOXYLPORPHYRINS

< or =10 nmol/24 hours

COPROPORPHYRINS (tetracarboxyl)

Males: < or =230 nmol/24 hours

Females: < or =168 nmol/24 hours

PORPHOBILINOGEN

< or =2.2 mc mol/24 hours

Porphyrias, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias: erythropoietic protoporphyria (EPP), X-linked dominant poroporphryia (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly sporadic (acquired) but in about 25% of cases it is inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. In addition, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of, uroporphyrin and or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

Useful For: Preferred test during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when the specimen will be received at Mayo Medical Laboratories within 72 hours of collection. If it will be longer, PQNU / Porphyrins, Quantitative, 24 Hour, Urine should be ordered. Preferred test to begin assessment for congenital erythropoietic porphyria and porphyria cutanea tarda

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach 1 of the laboratory directors in case the referring physician has additional
Reference Values:
UROPORPHYRINS (octacarboxyl)
< or =30 nmol/L

HEPTACARBOXYLPORPHYRINS
< or =7 nmol/L

HEXACARBOXYLPORPHYRINS
< or =2 nmol/L

PENTACARBOXYLPORPHYRINS
< or =5 nmol/L

COPROPORPHYRINS (tetracarboxyl)
< or =110 nmol/L

PORPHOBILINOGEN
< or =1.3 mcmol/L

See The Heme Biosynthetic Pathway in Special Instructions.


Porphyrias, Total, Plasma

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrinia cutanea tarda (PCT), and the erythropoietic porphyrias including erythropoietic protoporphyrinia (EPP), X-linked dominant protoporphyrinia (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyrinia caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and can be either sporadic (acquired) or inherited in an autosomal dominant manner. The
most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and alopecia may develop at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) occurs when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Plasma porphyrins are most appropriate for monitoring treatment of PCT. Although analysis in plasma is not recommended for diagnosis, increases in plasma porphyrin concentrations are observed in the cutaneous porphyrias and may be elevated during acute episodes of AIP, VP, and HCP. In addition, persons in chronic renal failure who develop bullous dermatosis similar to that associated with PCT may have increased plasma porphyrins. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

Useful For: Monitoring treatment of patients with porphyria cutanea tarda

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
< or =1.0 mcg/dL


POSA 89591

Posaconazole, Serum

Clinical Information: Posaconazole interferes with fungal cytochrome P450 (CYP) (lanosterol-14 alpha demethylase) activity, decreasing synthesis of ergosterol, the principal sterol in fungal cell membrane, and inhibiting fungal cell membrane formation.(1,3) Posaconazole has been approved for prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients (eg, hematopoietic stem cell transplant recipients with graft-versus-host disease: GVHD or those with prolonged neutropenia secondary to chemotherapy for hematologic malignancies) and treatment of oropharyngeal candidiasis (including patients refractory to itraconazole and/or fluconazole).(1,2) It also is approved for ocular administration (drug monitoring not required for this use). Posaconazole has a variable absorption. Food and liquid nutritional supplements increase absorption and fasting states do not provide sufficient absorption to ensure adequate plasma concentrations.(4,5) The drug has a high volume of distribution (Vd=465-1,774 L) and is highly protein bound (> or =97%), predominantly bound to albumin.(1,2) The drug does not undergo significant metabolism; approximately 15% to 17% undergoes non-CYP-mediated metabolism, primarily via hepatic glucuronidation into metabolites.(1) The half-life elimination is approximately 35 hours (range: 20-66 hours); steady-state is achieved after about 5 to 7 days. Time to maximum concentration is approximately 3 to 5 hours but, due to the highly variable absorption, trough level monitoring is recommended. Therapeutic drug monitoring should be considered in the following situations: -To document optimal absorption when used for prophylaxis or active treatment of a fungal infection -Consider rechecking a level even if initial level was in the goal range if
the patient: - Is unable to meet optimal nutritional intake - Is receiving continuous tube feeding - Is receiving a proton pump inhibitor (decreased posaconazole levels in some studies) - Has mucositis, diarrhea, vomiting, GVHD, or other reason that he/she may not absorb the drug well

**Useful For:** Monitoring of posaconazole therapy

**Interpretation:** Greater than 700 ng/mL (>0.7 mcg/mL) has been suggested for prophylaxis and also in a salvage trial for treatment of invasive Aspergillus infections.

**Reference Values:**
>700 ng/mL (trough)

**Clinical References:**

**POSV 9205**

**Post Vasectomy Check, Semen**

**Clinical Information:** Following a vasectomy, sperm may be found in the semen for 6 weeks to 3 months or longer. Regular ejaculation (every 3-4 days) may eliminate sperm from the reproductive tract more quickly. To check for the absence of sperm, semen should be evaluated for the presence of sperm 3 months postvasectomy and after a minimum of 20 ejaculations. Because the sperm count may be very low, the semen is centrifuged for concentration purposes. A negative result from 1 well-mixed postvasectomy semen specimen generally indicates that use of contraception is no longer necessary. Occasional cases have been reported where postvasectomy semen analysis (PVSA) shows intermittent presence of rare nonmotile sperm (RNMS) in the semen.(1)

**Useful For:** Determining absence or presence of sperm postvasectomy

**Interpretation:** Patients may stop using other methods of contraception when examination of 1 well-mixed postvasectomy semen specimen shows azoospermia or rare nonmotile sperm (RNMS < or = 100,000 nonmotile sperm/mL). The risk of pregnancy after vasectomy is approximately 1 in 2,000 for men who have postvasectomy azoospermia or postvasectomy semen analysis (PVSA) showing RNMS.(1) If >100,000 nonmotile sperm/mL persist beyond 6 months after vasectomy, then trends of serial PVSAs and clinical judgment should be used to decide whether the vasectomy is a failure and whether repeat vasectomy should be considered.(1) Vasectomy should be considered a failure if any motile sperm are seen on PVSA at 6 months after vasectomy, in which case repeat vasectomy should be considered.

**Reference Values:**
Zero sperm seen

**Clinical References:**

**PMSBB 81931**

**Postmortem Screening, Bile and Blood Spots**

**Clinical Information:** Postmortem screening involves acylcarnitine analysis in blood and bile specimens to evaluate cases of sudden or unexpected death. Acylcarnitine analysis enables the diagnosis of many disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs. Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and
provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry (MS/MS). Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and/or failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common viral infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor/vitamin supplementation. Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. Disorders Detectable by Acylcarnitine Analysis*: Fatty Acid Oxidation Disorders: -Short-chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency -Carnitine palmitoyl transferase type II (CPT-II) deficiency -Carnitine-acylcarnitine translocase (CACT) deficiency -Electron-Transferring Flavoproteins (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency: MADD; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic Acidemia -Methylmalonic Acidemia -Isovaleric Acidemia -3-Hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -Beta-ketothiolase deficiency -Malonic aciduria -Ethylmalonic encephalopathy *Further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than 1 condition. See Postmortem Screening Algorithm in Special Instructions. Refer to The Metabolic Autopsy: Postmortem Screening in Cases of Sudden, Unexpected Death, Mayo Medical Laboratories Communique 2003 Sep;28(9) for more information regarding diagnostic strategy.

**Useful For:** Postmortem evaluation of individuals at any age who died suddenly or unexpectedly; testing is particularly recommended under the following circumstances (risk factors): -Family history of sudden infant death syndrome or other sudden unexpected deaths at any age -Family history of Reye syndrome -Maternal complications of pregnancy (acute fatty liver pregnancy, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count]) -Lethargy, vomiting, fasting in the 48 hours prior to death -Allegation of child abuse (excluding obvious cases of trauma, physical harm) -Macroscopic findings at autopsy: - Fatty infiltration of the liver - Dilated or hypertrophic cardiomyopathy - Autopsy evidence of infection that routinely would not represent a life-threatening event

**Interpretation:** Reports of abnormal acylcarnitine profiles will include an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) as indicated, name and phone number of contacts who may provide these studies at Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not always sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) or molecular genetic analyses are required using additional tissue such as skin fibroblasts from the deceased patient. If not available, molecular genetic analysis of a patient's parents may enable the confirmation of a diagnosis.

**Reference Values:** Quantitative results are compared to a constantly updated range which corresponds to the 5 to 95 percentile interval of all postmortem cases analyzed in our laboratory.
**Clinical References:**

**NAK**

**Potassium and Sodium, Serum**

**Clinical Information:** See Individual Unit Codes

**Useful For:** See Individual Unit Codes

**Interpretation:** See Individual Unit Code

**Reference Values:**

**POTASSIUM**
- > or =12 months: 3.6-5.2 mmol/L
- Reference values have not been established for patients that are less than 12 months of age.

**SODIUM**
- > or =12 months: 135-145 mmol/L
- Reference values have not been established for patients that are less than 12 months of age.

**Clinical References:** See Individual Unit Codes

**KUR**

**Potassium, 24 Hour, Urine**

**Clinical Information:** Potassium (K+) is the major intracellular cation. Functions of potassium include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires that the body maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular is 20 times greater than the extracellular K+ concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute renal disease and end-stage renal failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of non-potassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

**Useful For:** Urine K+ is useful in determining the cause for hyper- or hypokalemia.

**Interpretation:** Hypokalemia reflecting true total body deficits of K+ can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is <30 mEq/d, it can be concluded that renal reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of >30 mEq/d in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.

**Reference Values:**
- 17-77 mmol/24 hours

**Potassium, Body Fluid**

**Clinical Information:** Potassium (K⁺) is the major cation of the intracellular fluid. Disturbance of potassium homeostasis has serious consequences. Decrease in extracellular potassium is characterized by muscle weakness, irritability, paralysis, fast heart rate, specific cardiac conduction effects that are apparent by electrocardiographic examination, and eventual cardiac arrest. More than 90% of hypertensive patients with aldosteronism have a hypokalemia (low K⁺). Low K⁺ also is common in vomiting, diarrhea, alcoholism, and folic acid deficiency. Abnormally high extracellular K⁺ levels produce symptoms of mental confusion; weakness, numbness and tingling of the extremities; weakness of the respiratory muscles; flaccid paralysis of the extremities; slowed heart rate, and eventually peripheral vascular collapse and cardiac arrest. Hyperkalemia may be seen in end stage renal failure, hemolysis, trauma, Addison's disease, metabolic acidosis, acute starvation, dehydration, and with rapid K⁺ infusion.

**Useful For:** Measurement of serum potassium is used for evaluation of electrolyte balance, cardiac arrhythmia, muscular weakness, hepatic encephalopathy, and renal failure. Potassium should be monitored during treatment of many conditions but especially in ketoacidosis of diabetes mellitus and any intravenous therapy for fluid replacement.

**Interpretation:** Plasma K⁺ values less than 3.0 mEq/L are associated with marked neuromuscular symptoms and are evidence of a critical degree of intracellular depletion. K⁺ values < 2.5 mEq/L are potentially life-threatening.

**Reference Values:** Not applicable

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**Potassium, Random, Urine**

**Clinical Information:** Potassium (K⁺) is the major intracellular cation. Functions of K⁺ include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K⁺ requires that the body maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular K⁺ concentration is 20 times greater than the extracellular concentration. Only 2% of total body K⁺ circulates in the plasma. The kidneys provide the most important regulation of K⁺. The proximal tubules reabsorb almost all the filtered K⁺. Under the influence of aldosterone, the remaining K⁺ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K⁺ excretion. Decreased excretion of K⁺ in acute renal disease and end-stage renal failure are common causes of prolonged hyperkalemia. Renal losses of K⁺ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of nonpotassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

**Useful For:** Determining the cause for hyper- or hypokalemia

**Interpretation:** Hypokalemia reflecting true total body deficits of potassium (K⁺) can be classified into renal and nonrenal losses based on the daily excretion of K⁺ in the urine. During hypokalemia, if urine excretion of K⁺ is <30 mEq/d, it can be concluded that renal reabsorption of K⁺ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K⁺ intake or extra renal loss of K⁺ rich fluid. Urine excretion of >30 mEq/d in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K⁺.

**Reference Values:** No established reference values

Potassium, Serum

Clinical Information: Potassium is the major cation of the intracellular fluid. Disturbance of potassium homeostasis has serious consequences. Decreases in extracellular potassium are characterized by muscle weakness, irritability, and eventual paralysis. Cardiac effects include tachycardia, other cardiac conduction abnormalities that are apparent by electrocardiographic examination, and eventual cardiac arrest. Hypokalemia (low potassium) is common in vomiting, diarrhea, alcoholism, and folic acid deficiency. Additionally, >90% of hypertensive patients with aldosteronism have hypokalemia. Abnormally high extracellular potassium levels produce symptoms of mental confusion; weakness, numbness and tingling of the extremities; weakness of the respiratory muscles; flaccid paralysis of the extremities; slowed heart rate; and eventually peripheral vascular collapse and cardiac arrest. Hyperkalemia may be seen in end-stage renal failure, hemolysis, trauma, Addison's disease, metabolic acidosis, acute starvation, dehydration, and with rapid potassium infusion.

Useful For: Evaluation of electrolyte balance, cardiac arrhythmia, muscular weakness, hepatic encephalopathy, and renal failure. Potassium should be monitored during treatment of many conditions but especially in diabetic ketoacidosis and any intravenous therapy for fluid replacement.

Interpretation: Potassium levels <3.0 mmol/L are associated with marked neuromuscular symptoms and are evidence of a critical degree of intracellular depletion. Potassium levels <2.5 mmol/L are potentially life-threatening. High potassium can be an acute medical emergency, particularly if the potassium increases over a short period of time. At values >6.0 mmol/L, symptoms are typically apparent. Potassium levels >6.0 mmol/L are potentially life-threatening. Levels >10.0 mmol/L are, in most cases, fatal.

Reference Values:
> or =12 months: 3.6-5.2 mmol/L
Reference values have not been established for patients that are less than 12 months of age.


Potato White IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Poultry and Meat Panel IgG

Interpretation: Beef IgG <2.0 mcg/mL Chicken IgG <2.0 mcg/mL Egg White IgG <2.0 mcg/mL Egg Yolk IgG <2.0 mcg/mL Lamb/Mutton IgG <2.0 mcg/mL Pork IgG <2.0 mcg/mL Turkey IgG <2.0 mcg/mL The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in
Variegate porphyria (VP) is an autosomal dominant (AD) cutaneous porphyria that can present with or without acute attacks that phenocopy acute intermittent porphyria (AIP). The most common clinical presentation of VP is increased photosensitivity, blistering, hyperpigmentation, and skin fragility in sun-exposed areas. The acute attacks of VP can include abdominal pain, vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. Cutaneous manifestations include edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases patients present with isolated photosensitivity. Variigate porphyria is caused by mutations in the PPOX gene. Mutations are typically inherited in an autosomal dominant fashion with incomplete penetrance, although homozygous mutations have been reported in association with a more severe clinical phenotype in early childhood. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in distinguishing variegate porphyria from AIP and hereditary coproporphyria.

**Useful For:** Confirmation of variegate porphyria for patients with clinical and biochemical features of the disease

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Clinical References:**

**Prader-Willi/Angelman Syndrome, Molecular Analysis**

**Clinical Information:** Prader-Willi syndrome (PWS) is a congenital disorder characterized by a biphasic clinical course. Neonates with PWS are hypotonic, have a weak cry, and are poor feeders, but improve over time. In later infancy and childhood, individuals with PWS have global developmental delay, short stature, hypogonadism, small hands and feet, and marked hyperphagia leading to obesity. PWS is thought to be due to loss of function of paternally expressed genes, although specific genes have not yet been definitively implicated in the phenotype of PWS. Etiology of Prader-Willi syndrome:
- Chromosome 15 deletion (15q11-13): approximately 70% to 75%
- Maternal uniparental disomy (UPD): 20% to 30%
- Imprinting defect: 1% to 5%
- Chromosome rearrangement: rare

The phenotype caused by paternal deletions of 15q11-13 and by maternal UPD are generally identical with the exception of relative hypopigmentation being more common in patients with deletion PWS. Angelman syndrome (AS) is a nonprogressive congenital disorder characterized by more significant developmental delay and mental retardation, ataxia, seizures, jerky arm movements, macrostomia, tongue thrusting, unprovoked laughter, brachycephaly, and virtual absence of speech. AS is due to loss of function of the maternally expressed gene UBE3A. Etiology of Angelman syndrome:
- Chromosome 15 deletion (15q11-13): approximately 70% to 75%
- Paternal UPD: approximately 5%
- UBE3A mutation: approximately 10%

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800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
defect: 2% to 5% - Chromosome rearrangement: rare - Unknown: approximately 10% The phenotype of AS patients with maternal deletions is generally more severe than that associated with paternal UPD or imprinting defects, including a higher rate or severity of microcephaly, seizures, and motor difficulties. Patients with AS caused by parental UPD or imprinting defects generally show better growth and higher developmental and language abilities. Both chromosome 15 deletions and UPD most often occur as de novo events during conception and, thus, recurrence risk to siblings is very low. In rare cases, chromosome 15 deletions and UPD occur as a result of parental translocations or other rare cytogenetic rearrangements, and in these cases recurrence risks to siblings are increased. The recurrence risk associated with imprinting defects is dependent on whether or not there is an identifiable mutation. UBE3A mutations can occur sporadically or be inherited in an autosomal dominant fashion. There is a 50% recurrence risk to siblings in cases of an inherited UBE3A mutation. Due to the complex genetic etiology of PWS and AS and the corresponding variability in recurrence risks, careful cytogenetic and molecular testing and family assessment are necessary to provide accurate genetic counseling. Initial studies to rule-out PWS or AS should include high-resolution cytogenetic analysis to identify chromosome abnormalities that may have phenotypic overlap with PWS or AS, and methylation-sensitive multiple ligation-dependent probe amplification (MLPA) to identify deletions, duplications, and methylation defects. In cases where methylation-sensitive MLPA suggests neither deletion or duplication, FISH can be used to confirm type I and type II deletions or characterize the disease mechanism, respectively. In cases where methylation-sensitive MLPA suggests abnormal methylation in the absence of a deletion or duplication, UPD studies can be used to characterize the disease mechanism. Assessment of patients found to have a deletion in the PWS/AS critical region on routine cytogenetic analysis includes confirmation of the deletion by FISH analysis and MLPA analysis to define parent of origin. See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions for more information.

Useful For: Confirmation of diagnosis in patients suspected of having either Prader-Willi syndrome (PWS) or Angelman syndrome (AS) based on clinical assessment or previous laboratory analysis Prenatal diagnosis in families at risk for PWS/AS

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

**PALB 9005**

**Prealbumin (PAB), Serum**

Clinical Information: Prealbumin is synthesized in the liver and acts as a binding protein for thyroxine and retinol-binding protein. The serum concentration of prealbumin reflects the synthesis capacity of the liver and is markedly diminished in malnutrition and other conditions. Due to its short half-life of approximately 2 days, prealbumin can be used for monitoring the nutritional status and efficacy of parenteral nutrition.

Useful For: Assessing nutritional status, especially in monitoring the response to nutritional support in the acutely ill patient

Interpretation: Values of 0 to 5 mg/dL, 5 to 10 mg/dL, and 10 to 15 mg/dL indicate severe, moderate, and mild protein depletion.

Reference Values:

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**Pregabalin (Lyrica)**

**Reference Values:**

- **Units:** ug/mL
- **Therapeutic and toxic ranges have not been established.**
- **Expected steady state pregabalin concentrations in patients taking recommended daily dosages: up to 10 ug/mL.**

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**Pregnenolone and 17-Hydroxypregnenolone**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxyxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** An ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out. Confirming a diagnosis of 3-beta-hydroxy dehydrogenase (3-beta-HSD) deficiency and 17-alpha-hydroxylase deficiency. Analysis for 17-hydroxypregnenolone is also useful as part of a battery of tests to evaluate females with hirsutism or infertility. Both can result from adult-onset CAH.

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold
elevations. 17-OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxyprogrenenolone and pregnenolone and DHEA levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as seen in CYP21A2 mutation, and cortisol also is low, but 17-OHPG is only mildly, if at all, elevated. In the also very rare 17-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenenolone, 17-OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**

**PREGNENOLONE**

**CHILDREN***

**Males**

- 0-6 years: not established
- 7-9 years: <206 ng/dL
- 10-12 years: <152 ng/dL
- 13-15 years: 18-197 ng/dL
- 16-17 years: 17-228 ng/dL

**Tanner Stages**

- Stage I: <157 ng/dL
- Stage II: <144 ng/dL
- Stage III: <215 ng/dL
- Stage IV-V: 19-201 ng/dL

**Females**

- 0-6 years: not established
- 7-9 years: <151 ng/dL
- 10-12 years: 19-220 ng/dL
- 13-15 years: 22-210 ng/dL
- 16-17 years: 22-229 ng/dL

**Tanner Stages**

- Stage I: <172 ng/dL
- Stage II: 22-229 ng/dL
- Stage III: 34-215 ng/dL
- Stage IV-V: 26-235 ng/dL

**ADULTS**

> or =18 years: 33-248 ng/dL


**17-HYDROXYPREGNENOLONE**

**CHILDREN***

**Males**

- Premature (26-28 weeks): 1,219-9,799 ng/dL
- Premature (29-36 weeks): 346-8,911 ng/dL
- Full term (1-5 months): 229-3,104 ng/dL
- 6 months-364 days: 221-1,981 ng/dL
- 1-2 years: 35-712 ng/dL
- 3-6 years: <277 ng/dL
- 7-9 years: <188 ng/dL
- 10-12 years: <393 ng/dL
- 13-15 years: 35-465 ng/dL
- 16-17 years: 32-478 ng/dL

**Tanner Stages**

- Stage I: <209 ng/dL
Stage II: <356 ng/dL  
Stage III: <451 ng/dL  
Stage IV-V: 35-478 ng/dL

Females  
Premature (26-28 weeks): 1,219-9,799 ng/dL  
Premature (29-36 weeks): 346-8,911 ng/dL  
Full term (1-5 months): 229-3,104 ng/dL  
6 months-364 days: 221-1,981 ng/dL  
1-2 years: 35-712 ng/dL  
3-6 years: <277 ng/dL  
7-9 years: <213 ng/dL  
10-12 years: <399 ng/dL  
13-15 years: <408 ng/dL  
16-17 years: <424 ng/dL  

**Tanner Stages**  
Stage I: <236 ng/dL  
Stage II: <368 ng/dL  
Stage III: <431 ng/dL  
Stage IV-V: <413 ng/dL

**ADULTS**  
**Males**  
> or =18 years: 55-455 ng/dL  
**Females**  
> or =18 years: 31-455 ng/dL


**Clinical References:**  

**Pregnenolone, Serum**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is...
decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

Useful For: An ancillary test for congenital adrenal hyperplasia, particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase deficiency

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-Hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxypregnenolone and pregnenolone and dehydroepiandrosterone levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as seen in CYP21A2 mutation, and cortisol also is low, but 17-OHPG is only mildly, if at all, elevated. In the also very rare 17-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, 17-OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-dexycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

Reference Values:
CHILDREN*
Males
0-6 years: not established
7-9 years: <206 ng/dL
10-12 years: <152 ng/dL
13-15 years: 18-197 ng/dL
16-17 years: 17-228 ng/dL
Tanner Stages
Stage I: <157 ng/dL
Stage II: <144 ng/dL
Stage III: <215 ng/dL
Stage IV-V: 19-201 ng/dL
Females
0-6 years: not established
7-9 years: <151 ng/dL
10-12 years: 19-220 ng/dL
13-15 years: 22-210 ng/dL
16-17 years: 22-229 ng/dL
Tanner Stages
Stage I: <172 ng/dL
Stage II: 22-229 ng/dL
Stage III: 34-215 ng/dL
Stage IV-V: 26-235 ng/dL

ADULTS
> or =18 years: 33-248 ng/dL
FPAP2 91198

**Premature Adrenarche Profile II (Androstenedione, DHEA, 17-OH-Pregnenolone, 17-Alpha-Hydroxyprogesterone, Testosterone)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione, Mass Spec</td>
<td></td>
</tr>
<tr>
<td>Units: ng/dL</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Range</td>
</tr>
<tr>
<td>Premature (26-28w)</td>
<td>63-935</td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
</tr>
<tr>
<td>Premature (31-35w)</td>
<td>50-449</td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
</tr>
<tr>
<td>Full Term (1-7 days)</td>
<td>&lt;10-279</td>
</tr>
</tbody>
</table>

Levels decrease rapidly to <52 ng/dL after one week.

1-11m <10-37

Androstenedione gradually decreases during the first six months to prepubertal levels.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal Children:</td>
<td>&lt;10-17</td>
</tr>
<tr>
<td>Adult Males</td>
<td>44-186</td>
</tr>
<tr>
<td>Adult Females</td>
<td>28-230</td>
</tr>
<tr>
<td>Females Postmenopausal</td>
<td>&lt;10-93</td>
</tr>
<tr>
<td>Females Tanner Stages</td>
<td>Age (years)</td>
</tr>
<tr>
<td>1</td>
<td>&lt;9.2</td>
</tr>
<tr>
<td>2</td>
<td>9.2-13.7</td>
</tr>
<tr>
<td>3</td>
<td>10.0-14.4</td>
</tr>
<tr>
<td>4</td>
<td>10.7-15.6</td>
</tr>
<tr>
<td>5</td>
<td>11.8-18.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males Tanner Stages</td>
<td>Age (years)</td>
</tr>
<tr>
<td>1</td>
<td>&lt;9.8</td>
</tr>
<tr>
<td>2</td>
<td>9.8-14.5</td>
</tr>
<tr>
<td>3</td>
<td>10.7-15.4</td>
</tr>
<tr>
<td>4</td>
<td>11.8-16.2</td>
</tr>
<tr>
<td>5</td>
<td>12.8-17.3</td>
</tr>
</tbody>
</table>

Dehydroepiandrosterone (DHEA)
### 17-OH Pregnenolone, Mass Spec

**Units:** ng/dL  
**Range:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>375 - 3559</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>64 - 2380</td>
</tr>
<tr>
<td>3 Days</td>
<td>10 - 829</td>
</tr>
<tr>
<td>1 - 5m</td>
<td>36 - 763</td>
</tr>
<tr>
<td>6 - 11m</td>
<td>42 - 540</td>
</tr>
<tr>
<td>12 - 23m</td>
<td>14 - 207</td>
</tr>
<tr>
<td>24m-5y</td>
<td>10 - 103</td>
</tr>
<tr>
<td>6 - 9y</td>
<td>10 - 186</td>
</tr>
<tr>
<td>Pubertal</td>
<td>44 - 235</td>
</tr>
<tr>
<td>Adults</td>
<td>53 - 357</td>
</tr>
</tbody>
</table>

**17-Alpha-Hydroxyprogesterone**  
**Units:** ng/dL  
**Range:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>124 - 841</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>26 - 568</td>
</tr>
<tr>
<td>Full-Term Day 3</td>
<td>&lt;78</td>
</tr>
</tbody>
</table>

**Males**

Levels increase after the first week to peak values ranging from 40-200 ng/dL between 30 and 60 days. Values then decline to a prepubertal value of <91 before one year.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>&lt;91</td>
</tr>
<tr>
<td>Adult Males</td>
<td>27 - 199</td>
</tr>
</tbody>
</table>

**Females**

(1 - 11 Months)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 - 106</td>
<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td>&lt;91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>15 - 70</td>
</tr>
<tr>
<td>Luteal</td>
<td>35 - 290</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.2</td>
</tr>
<tr>
<td>2</td>
<td>9.2-13.7</td>
</tr>
<tr>
<td>3</td>
<td>10.0-14.4</td>
</tr>
<tr>
<td>4</td>
<td>10.7-15.6</td>
</tr>
<tr>
<td>5</td>
<td>11.8-18.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
</tr>
<tr>
<td>2</td>
<td>9.8-14.5</td>
</tr>
<tr>
<td>3</td>
<td>10.7-15.4</td>
</tr>
</tbody>
</table>
Testosterone, Serum (Total)

<table>
<thead>
<tr>
<th>Units: ng/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Premature (26-28w) Day 4</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
</tr>
<tr>
<td>Newborns</td>
</tr>
<tr>
<td>1 - 7m: Levels decrease rapidly the first week to 20-50, then increase to 60-400 between 20-60 days. Levels then decline to prepubertal range levels of &lt;2.5 - 10 by seven months.</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Premature (26 - 28w) Day 4</td>
</tr>
<tr>
<td>Premature (31 - 35w) Day 4</td>
</tr>
<tr>
<td>Newborns</td>
</tr>
<tr>
<td>1 - 7m: Levels decrease during the first month to less than 10 and remain there until puberty.</td>
</tr>
</tbody>
</table>

Prepubertal Males and Females | <2.5 - 10 ng/dL |

<table>
<thead>
<tr>
<th>Adult Males</th>
<th>&gt;18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>348 - 1197</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adult Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal:</td>
</tr>
<tr>
<td>10 - 55</td>
</tr>
<tr>
<td>Postmenopausal:</td>
</tr>
<tr>
<td>7 - 40</td>
</tr>
</tbody>
</table>

Males

<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Age (years)</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.8</td>
<td>&lt;2.5 - 10</td>
</tr>
<tr>
<td>2</td>
<td>9.8 - 14.5</td>
<td>18 - 150</td>
</tr>
<tr>
<td>3</td>
<td>10.7 - 15.4</td>
<td>100 - 320</td>
</tr>
<tr>
<td>4</td>
<td>11.8 - 16.2</td>
<td>200 - 620</td>
</tr>
<tr>
<td>5</td>
<td>12.8 - 17.3</td>
<td>350 - 970</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Age (years)</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;9.2</td>
<td>&lt;2.5 - 10</td>
</tr>
<tr>
<td>2</td>
<td>9.2 - 13.7</td>
<td>7 - 28</td>
</tr>
<tr>
<td>3</td>
<td>10.0 - 14.4</td>
<td>15 - 35</td>
</tr>
<tr>
<td>4</td>
<td>10.7 - 15.6</td>
<td>13 - 32</td>
</tr>
<tr>
<td>5</td>
<td>11.8 - 18.6</td>
<td>20 - 38</td>
</tr>
</tbody>
</table>

Prenatal Aneuploidy Detection, FISH

Clinical Information: Approximately half of clinically recognizable spontaneous abortions have a major chromosomal anomaly. Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8/1,000 have a major chromosome anomaly, of which 6.5/1,000 involve aneuploidy of the 5 chromosomes analyzed by this test. Therefore, aneuploidy of chromosomes 13, 18, 21, X, and Y accounts for 81% to 95% of major chromosome anomalies in liveborn infants. Techniques to detect aneuploidy include standard chromosome analysis and FISH. Standard chromosome analysis from amniotic fluid cells or chorionic villi requires 5 to 9 days for culture, harvest, and analysis. FISH, which uses DNA probes and can be performed on cultured and uncultured cells, can rapidly detect aneuploidy of 13, 18, 21, X, and Y in uncultured amniotic fluid cells or chorionic villi. FISH-based analysis may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes. This test does not detect aneuploidy of chromosomes other than 13, 18, 21, X, or Y. This...
test does not detect other chromosomal or structural anomalies. Low levels of mosaicism involving chromosomes 13, 18, 21, X, or Y may not be detected by this procedure. There may be interpretation problems in cases of maternal cell contamination.

**Useful For:** Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in prenatal specimens

**Interpretation:** An interpretive report is provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

---

**Prenatal Hepatitis Evaluation**

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic; others may develop chronic liver disease including cirrhosis and hepatocellular carcinoma. HBV is spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles by drug addicts). The virus is found in virtually every type of human body fluid and also is spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy.

**Useful For:** Screening pregnant women for chronic hepatitis B Determining the level of infectivity of chronic hepatitis B in pregnant women

**Interpretation:** Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. A confirmed positive result for HBsAg is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Hepatitis B envelope antigen (HBeAg) appears at approximately the same time as HBsAg and indicates that the virus is replicating and the individual is infectious. Appearance of hepatitis Be antibody (anti-HBe) after the disappearance of HBsAg and HBeAg usually indicates recovery and loss of infectivity.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

---

**Previous Hepatitis (Unknown Type)**

**Clinical Information:** Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of the viral hepatitis in United States adults. HAV infection is spread by the oral/fecal route and produces acute hepatitis which follows a benign, self-limited course. Spread of the disease is usually
associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and in institutions or high density centers such as prisons and health care centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products, eg, blood transfusion, sharing of needles by drug addicts. The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these chronic carriers are asymptomatic, others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. See Advances in the Laboratory Diagnosis of Hepatitis C (2002) in Publications in Special Instructions. See HBV Infection-Diagnostic Approach and Management Algorithm and Testing Algorithm for the Diagnosis of Hepatitis C in Special Instructions.

Useful For: Determining if an individual has been infected following exposure to an unknown type of hepatitis Obtaining baseline serologic markers of an individual exposed to a source with an unknown type of hepatitis Determining immunity to hepatitis A and B viral infections

Interpretation: Hepatitis A: Antibody against hepatitis A antigen (anti-HAV) is almost always detectable by the onset of symptoms (usually 15-45 days after exposure). The initial antibody consists almost entirely of the IgM subclass of antibody. Anti-HAV IgM usually falls to undetectable levels 3 to 6 months after infection. Anti-HAV, IgG levels rise quickly once the virus is cleared and persist for many years. Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. Hepatitis C: Hepatitis C virus antibody (anti-HCV) is usually not detectable during the early months following infection, but is almost always detectable by the late convalescent stage of infection. Anti-HCV is not neutralizing and does not provide immunity.

Reference Values:
HEPATITIS B SURFACE ANTIGEN
Negative (reported as reactive, positive or negative)

HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE
Hepatitis B Surface Antibody
Unvaccinated: negative
Vaccinated: positive
Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <5.0 mIU/mL
Vaccinated: > or =12.0 mIU/mL

HEPATITIS B CORE ANTIBODY
Negative (reported as positive or negative)

HEPATITIS A ANTIBODY, TOTAL
Negative (reported as positive or negative)

HEPATITIS C VIRUS ANTIBODY
Negative (reported as reactive or negative)
HEPATITIS C VIRUS, RT-PCR
Negative for HCV-RNA
If positive, reported as positive for HCV-RNA

HEPATITIS BS ANTIGEN CONFIRMATION
Negative (reported as positive or negative)

bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


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**PROC G 37055**

**Procainamide and N-acetylprocainamide, Serum**

**Clinical Information:** Procainamide (PA) is indicated in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia. PA is contraindicated in patients with complete atrioventricular block. PA is metabolized to an active metabolite, N-acetylprocainamide (NAPA), with metabolism controlled by genetically determined enzymes. In patients with normal renal function, fast metabolizers will have a PA:NAPA ratio <1 at 3 hours after the dose is administered. Slow acetylators (PA:NAPA ratio >2 after 3 hours) are more likely to develop a positive test for antinuclear antibodies and present with systemic lupus erythematosus-like symptoms. Patients who have prolonged exposure to procainamide >12 mcg/mL or NAPA concentration > or =40.0 mcg/mL are very likely to exhibit symptoms of toxicity that are characterized by hypotension, ventricular fibrillation, widened QRS complex, junctional tachycardia, oliguria, confusion, nausea, and vomiting. Renal disease, hepatic disease, cardiac failure, and states of low cardiac output reduce the metabolism and clearance of PA and NAPA. Coadministration of histamine H2 receptor antagonists, such as cimetidine and ranitidine reduce renal clearance of PA and NAPA resulting in higher plasma concentrations of each.

**Useful For:** Monitoring therapy with procainamide Assessing compliance Evaluating toxicity

**Interpretation:** Administration of a dose of 50 mg/kg will usually yield the optimal trough concentration in the range of 4.0 to 10.0 mcg/mL for procainamide and 12.0 to 18.0 mcg/mL for N-acetylprocainamide.

**Reference Values:**
Procainamide
Therapeutic: 4.0-10.0 mcg/mL
Critical value: >12.0 mcg/mL

N-acetylprocainamide
Therapeutic: 12.0-18.0 mcg/mL
Critical value: >=40.0 mcg/mL


PCT
83169

Procalcitonin, Serum

Clinical Information: Procalcitonin (ProCT) is a 116 amino acid precursor of calcitonin (CT). ProCT is processed to an N-terminal 57 amino acid peptide (CT [32 amino acids] and a 21 amino acid C-terminal peptide, catacalcin [CCP-1]). Expression of this group of peptides is normally limited to thyroid C cells and, to a small extent, other neuroendocrine cells. CT is the only hormonally active of these peptides. CT is secreted by C cells in response to hypercalcemia and inhibits bone resorption by osteoclasts, minimizing oscillations in serum calcium and calcium loss. During severe systemic inflammation, in particular related to bacterial infection, the tissue specific control of CT-related peptides expression breaks down and ProCT and CCP-1 (referred collectively to as ProCT) are secreted in large quantities by many tissues. CT levels do not change. Noninfectious inflammatory stimuli need to be extremely severe to result in ProCT elevations, making it a more specific marker for severe infections than most other inflammatory markers (cytokines, interleukins, and acute-phase reactants). ProCT elevations are also more sustained than those of most other markers and occur in neutropenic patients. This reduces the risk of false-negative results. ProCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours. ProCT secretion parallels closely the severity of the inflammatory insult, with higher levels associated with more severe disease and declining levels with resolution of illness. In the absence of an ongoing stimulus, ProCT is eliminated with a half-life of 24 to 35 hours, making it suitable for serial monitoring. Finally, the dependence of sustained ProCT elevations on ongoing inflammatory stimuli allows identification of secondary septic events in conditions that can result in noninfectious ProCT elevations, such as cardiac surgery, severe trauma, severe burns, and multiorgan failure. ProCT levels should fall at a predictable pace in the absence of secondary infection.

Useful For: Diagnosis of bacteremia and septicemia in adults and children (including neonates) Diagnosis of renal involvement in urinary tract infection in children Diagnosis of bacterial infection in neutropenic patients Diagnosis, risk stratification, and monitoring of septic shock Diagnosis of systemic secondary infection post-surgery, and in severe trauma, burns, and multiorgan failure Differential diagnosis of bacterial versus viral meningitis Differential diagnosis of community-acquired bacterial versus viral pneumonia Monitoring of therapeutic response to antibacterial therapy

Interpretation: General considerations: -In children older than 72 hours and in adults, levels <0.15 ng/mL make a diagnosis of significant bacterial infection unlikely. -Procalcitonin (ProCT) between 0.15 and 2.0 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. -Levels >2.0 ng/mL are highly suggestive of systemic bacterial infection/sepsis or severe localized bacterial infection, such as severe pneumonia, meningitis, or peritonitis. They can also occur after severe noninfectious inflammatory stimuli such as major burns, severe trauma, acute multiorgan failure, or major abdominal or cardiothoracic surgery. In cases of noninfectious elevations, ProCT levels should begin to fall after 24 to 48 hours. -Autoimmune diseases, chronic inflammatory processes, viral infections, and mild localized bacterial infections rarely lead to elevations of ProCT of >0.5 ng/mL. Specific diagnostic applications, based on the current consensus in the literature: -Diagnosis of bacteremia in neonates: After birth ProCT values increase from birth to reach peak values at about 24 hours of life and the decrease gradually by 48 hours of life. Therefore, during the first 72 hours of life different reference ranges will apply to newborn infants at different hours of age. ProCT levels on newborns suffering from early sepsis are significantly higher than those of noninfected newborns when reference ranges by hours of age are used.(1,2) Adult levels should apply at >=72
hours after birth. -Diagnosis of renal involvement in pediatric urinary tract infections: In children with urinary tract infections, a ProCT level of >0.5 ng/mL has a 70% to 90% sensitivity and an 80% to 90% specificity for renal involvement. -ProCT responses in neutropenic patients are similar to patients with normal neutrophil counts and function, and the cutoffs discussed under general considerations above should be used. In the appropriate clinical setting, ProCT levels above 2.0 ng/mL on the first day of admission to the intensive care unit (ICU) represent a high risk for progression to severe sepsis and/or septic shock. ProCT levels below 0.5 ng/mL on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock. Reported sensitivity and specificity for the diagnosis of sepsis range from 60% to 100%, depending on underlying and coexisting diseases and the patient populations studied. The higher the ProCT level the worse the prognosis. A ProCT level of <0.5 ng/mL makes bacterial meningitis very unlikely. Most patients with bacterial meningitis will have ProCT levels of >10 times this level. With successful antibiotic therapy, ProCT levels should fall with a half-life to 24 to 35 hours.

Reference Values:
- Adults and children > or =72 hours: < or =0.15 ng/mL
- Children < 72 hours: <2.0 ng/mL at birth, rises to < or =20 ng/mL at 18-30 hours of age, then falls to < or =0.15 ng/mL by 72 hours of age

Clinical References:

Procollagen I Intact N-Terminal, Serum

Clinical Information: Procollagen type I propeptides are derived from collagen type I, which is the most common collagen type found in mineralized bone. In bone, collagen is synthesized by osteoblasts in the form of procollagen. This precursor contains a short signal sequence and terminal extension peptides: amino-terminal propeptide (PINP) and carboxy-terminal propeptide. These propeptide extensions are removed by specific proteinases before the collagen molecules form. Both propeptides can be found in the circulation and their concentration reflects the synthesis rate of collagen type I. Although collagen type I propeptides may also arise from other tissues (such as the skin, vessels, fibrocartilage, and tendons), most nonskeletal tissues exhibit a slower turnover than bone, and contribute very little to the circulating pool of PINP. PINP is considered the most sensitive marker of bone formation and it is particularly useful for monitoring bone formation therapies and antiresorptive therapies; it is recommended that the test be performed at baseline before starting osteoporosis therapy and again 3 to 6 months later. PINP could be detected in the circulation as the "intact" or trimeric molecule and the monomer. In osteoporosis subjects with normal renal function, the predominant form of PINP detected in circulation is the trimeric form. However, monomeric PINP fragments may accumulate in patients with renal failure or metastatic bone disease.

Useful For: An aid in monitoring antiresorptive and anabolic therapy in patients with osteoporosis An adjunct in the assessment of conditions associated with increased bone turnover such as Paget disease

Interpretation: This test should be performed before beginning osteoporosis treatment (i.e., prior to the start of therapy) to establish a baseline procollagen I intact N-terminal (PINP) level. Three to 6 months after initiation of therapy, a change of > or =21% (least significant change) from baseline PINP levels indicates an adequate therapeutic response. This assay is specific for the intact trimeric form of PINP. The direction of the change in PINP levels (decrease or increase) will depend on the type of osteoporosis.
treatment. In patients taking bisphosphonates, PINP levels have been shown to decrease up to 70% from baseline after 6 months of therapy. Treatment with hormone replacement therapy also shows a decrease in PINP levels, but to a lesser degree than bisphosphonates therapy. In patients treated with teriparatide (recombinant human parathyroid hormone 1-34), PINP levels increase from baseline reflecting the stimulatory effect of teriparatide on osteoblasts and bone formation. PINP levels have been shown to significantly increase as early as 1 month after teriparatide treatment, peaking at 6 months following treatment. Increases of >10 mcg/L have been reported in 77% to 79% of teriparatide-treated patients after 3 months of therapy and are considered a successful response.

Reference Values:
Reference values have not been established for patients who are <18 years of age.
Adult male: 22-87 mcg/L
Adult female premenopausal: 19-83 mcg/L
Adult female postmenopausal: 16-96 mcg/L


POCRF 35295

Products of Conception (POC) Aneuploidy Detection, FISH, Fresh Tissue

Clinical Information: This test is appropriate for analysis for aneuploidies of chromosomes 13, 15, 16, 18, 21, 22, X and Y in products of conception, spontaneous abortions, stillborn infants, or neonates. Products of conception (POC) are tissues created at conception that spontaneously miscarry; these tissues include chorionic villi, fetal membranes, or fetal tissue. Spontaneous miscarriages occur in 15% to 20% of all recognized human conceptions. While there are many possible causes for miscarriages, chromosome anomalies can be identified in up to 50% of first-trimester miscarriages. It is important to determine a possible chromosomal cause of the pregnancy loss as this information impacts patient management and facilitates understanding of the reason for the loss. Chromosomal aneuploidy, the gain or loss of chromosomes, is a major cause of early fetal demise. Trisomy is the most common type of chromosome abnormality in spontaneous abortions and has been observed for most chromosomes, with 13, 15, 16, 18, 21, 22, X, and Y being the most common. Conventional chromosome analyses of POC (CHRPC / Chromosome Analysis, Autopsy, Products of Conception, or Stillbirth) is a commonly performed method used to identify these common chromosome aneuploidies. Conventional chromosome analysis involves fibroblast cultures. Unfortunately, 20% of POC specimens fail to grow when cultured. A FISH method has been developed to analyze this subset of cases.

Useful For: Screening for chromosomal aneuploidies of chromosomes 13, 15, 16, 18, 21, 22, X, and Y in products of conception when the culture of fresh tissue is not successful

Interpretation: Aneuploidy is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.


POCF 35294

Products of Conception (POC) Aneuploidy Detection, FISH, Paraffin-Embedded Tissue
**Clinical Information:** Products of conception (POC) are tissues created at conception that spontaneously miscarry; these tissues include chorionic villi, fetal membranes, or fetal tissue. Spontaneous miscarriages occur in 15% to 20% of all recognized human conceptions. While there are many possible causes for miscarriages, chromosome anomalies can be identified in up to 50% of first-trimester miscarriages. It is important to determine a possible chromosomal cause of the pregnancy loss as this information impacts patient management and facilitates understanding of the reason for the loss. Chromosomal aneuploidy, the gain or loss of chromosomes, is a major cause of early fetal demise. Trisomy is the most common type of chromosome abnormality in spontaneous abortions and has been observed for most chromosomes, with 13, 15, 16, 18, 21, 22, X, and Y being the most common. Conventional chromosome analyses of POC (CHRPC / Chromosomes, Products of Conception/Fetal Loss) is a commonly performed method used to identify these common chromosome aneuploidies. Conventional chromosome analysis involves fibroblast cultures. Unfortunately, 20% of POC specimens fail to grow when cultured. A FISH method has been developed to analyze this subset of cases or to be used when fresh tissue is not available for full chromosome analysis.

**Useful For:** Screening for chromosomal aneuploidies of chromosomes 13, 15, 16, 18, 21, 22, X, and Y when fresh tissue is not available

**Interpretation:** Aneuploidy is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** Laurino MY, Bennett RL, Saraiya DS, et al: Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Couns 2005;14:165-181

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**Progestosterone, Serum**

**Clinical Information:** Sources of progesterone are the adrenal glands, corpus luteum, and placenta. Adrenal Glands: Progesterone synthesized in the adrenal glands is converted to other corticosteroids and androgens and, thus, is not a major contributor to circulating serum levels unless there is a progesterone-producing tumor present. Corpus Luteum: After ovulation, there is a significant rise in serum levels as the corpus luteum begins to produce progesterone in increasing amounts. This causes changes in the uterus, preparing it for implantation of a fertilized egg. If implantation occurs, the trophoblast begins to secrete human chorionic gonadotropin, which maintains the corpus luteum and its secretion of progesterone. If there is no implantation, the corpus luteum degenerates and circulating progesterone levels decrease rapidly, reaching follicular phase levels about 4 days before the next menstrual period. Placenta: By the end of the first trimester, the placenta becomes the primary secretor of progesterone.

**Useful For:** Ascertaining whether ovulation occurred in a menstrual cycle Evaluation of placental function in pregnancy Workup of some patients with adrenal or testicular tumors

**Interpretation:** Ovulation results in a mid-cycle surge of luteinizing hormone (LH) followed by an increase in progesterone secretion, peaking between day 21 and 23. If no fertilization and implantation has occurred by then, supplying the corpus luteum with human chorionic gonadotropin-driven growth stimulus, progesterone secretion falls, ultimately triggering menstruation. A day 21 to 23 serum progesterone peak of 6.5 to 7 ng/mL is the minimal level considered consistent with ovulation. A level in excess of 18 ng/mL is considered conclusive proof of ovulation. Placental insufficiency has been associated with low levels of LH and progesterone. Levels of LH and progesterone may be increased in some adrenal or testicular tumors.

**Reference Values:**
Males
- Cord blood: 569-1,107 ng/mL
- 0-23 months: 0.87-3.37 ng/mL

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
2-9 years: <0.15 ng/mL
10-17 years: adult levels are attained by puberty.*
> or =18 years: 0.20-1.40 ng/mL

Females
Cord blood: 569-1,107 ng/mL
0-23 months: 0.87-3.37 ng/mL
2-9 years: 0.20-0.24 ng/mL
10-17 years: values increase through puberty and adolescence.*

Premenopausal
Follicular phase: 0.20-1.50 ng/mL
Ovulation phase: 0.80-3.00 ng/mL
Luteal phase: 1.70-27.00 ng/mL
Postmenopausal: <0.15-0.80 ng/mL


**FPROG**
90287

**Progesterone, Urine**

**Clinical Information:** Progesterone is a Progestin produced primarily from enzymatic metabolism of Pregnenolone. It is enzymatically converted to 17-Hydroxy Progesterone and 11-Deoxycorticosterone. It is secreted by both the gonads and the adrenal glands. It is bound to Cortisol Binding Globulin and Albumin, but a small percentage is present in the "Free" bioactive form. It is excreted into the urine as its conjugated and unconjugated forms and as Pregnanediol (conjugated and unconjugated). This assay measures the conjugated and unconjugated forms of Progesterone. Progesterone is responsible for cellular changes in the cervix, vagina, and uterus. Levels are lowest in the follicular phase and increase rapidly following the luteal surge. Progesterone increases greatly during pregnancy. Measurement of Urine Progesterone can be useful to monitor fertility, corpus luteum function, endometrial development, and be helpful in in-vitro fertilization patients yielding an integrated look of Progesterone activity over a 24-hour period.

**Reference Values:**
- Adult Males: up to 0.5 ug/24 hours
- Adult Females: up to 2.8 ug/24 hours

**GRNZ**
35446

**Progranulin Gene (GRN), Full Gene Analysis**

**Clinical Information:** Frontotemporal lobar degeneration (FTLD) describes a group of neurodegenerative diseases that are frequent causes of dementia, accounting for 5% to 10% of all dementia patients and 10% to 20% of patients with onset of dementia before age 65. Frontotemporal dementia (FTD) is the most common clinical manifestation of FTLD. The clinical presentation of FTD is variable, but typically includes changes in personality and social conduct, often associated with impulse disinhibition, followed by more general cognitive decline, eventually leading to dementia. The age of onset is extremely variable ranging from 35 to 87 years. Duration of the disease ranges from 3 to 12 years. Based on the immunohistochemical staining, there are 2 main subtypes of FTLD: tau-positive FTLD and tau-negative FTLD with ubiquitin-positive inclusions (FTLD-U). Mutations in the MAPT gene have been identified in patients with tau-positive FTLD; mutations in the progranulin gene (GRN) have been identified in patients with FTLD-U. Both MAPT and GRN are located on chromosome 17q21, with GRN located only 1.7 Mb centromeric of MAPT. GRN consists of 12 coding and 1 noncoding exons. GRN
encodes progranulin, a multifunctional protein that plays a role in multiple processes including development, wound repair, and inflammation. The function of GRN in the brain is not well understood, but progranulin is widely expressed in neurons and glial cells. More than 40 different pathogenic GRN mutations have been reported. All pathogenic mutations identified to date create functional null alleles that result in decreased progranulin production, suggesting that reduced levels of progranulin may lead to neurodegeneration.

**Useful For:** Aiding the diagnosis of frontotemporal dementia Distinguishing frontotemporal dementia from other dementias, including Alzheimer dementia Identifying individuals who are at increased risk of frontotemporal dementia

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**PINS 80908**

**Proinsulin, Plasma**

**Clinical Information:** Proinsulin is the precursor of insulin and C-peptide. Following synthesis, proinsulin is packaged into secretory granules, where it is processed to C-peptide and insulin by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E. Only 1% to 3% of proinsulin is secreted intact. However, because proinsulin has a longer half-life than insulin, circulating proinsulin concentrations are in the range of 5% to 30% of circulating insulin concentrations on a molar basis, with the higher relative proportions seen after meals and in patients with insulin resistance or early type 2 diabetes. Proinsulin can bind to the insulin receptor and exhibits 5% to 10% of the metabolic activity of insulin. Proinsulin levels might be elevated in patients with insulin-producing islet cell tumors (insulinomas). These patients suffer from hypoglycemic attacks due to inappropriate secretion of insulin by the tumors. The biochemical diagnosis of insulinoma rests primarily on demonstrating non-suppressed insulin levels in the presence of hypoglycemia (blood glucose <45 mg/dL). The diagnosis can be difficult, as tumors might be small or secrete insulin only episodically. The use of hypoglycemic drugs (eg, sulfonylurea) or insulin injections can also mimic insulinoma. Diagnostic evaluations frequently require a prolonged fast (72 hours), as well as supplementary tests (in addition to insulin and glucose measurements) including a sulfonylurea screen and measurement of C-peptide, proinsulin and beta-hydroxybutyrate. The inappropriate over-secretion of insulin by insulinomas causes release of increased numbers of immature secretory granules with incompletely processed proinsulin, resulting in elevated serum/plasma proinsulin concentrations. This relative over-secretion of proinsulin insulinomas tends to be most marked in the fasting state, when proinsulin normally does not account for more than 5% of insulin concentrations on a molar basis. Proinsulin is strikingly elevated in PC1/3 deficiency. These patients have defects in the processing of multiple peptide hormones and suffer from diabetes, adrenal insufficiency, infertility, and obesity. Affected individuals typically have red hair regardless of racial background. Mutations in the proinsulin molecule have been reported that affect PC cleavage efficiency or subsequent proinsulin metabolism. These mutations can also lead to markedly elevated proinsulin levels, but are usually not accompanied by diabetes, or any other hormonal abnormalities.

**Useful For:** As part of the diagnostic workup of suspected insulinoma As part of the diagnostic workup of patients with suspected PC1/3 deficiency As part of the diagnostic workup of patients with suspected...
Interpretation: Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (20 pmol/L) when hypoglycemic (blood glucose <45-60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range. The sensitivity and specificity for a diagnosis of insulinoma during hypoglycemia are approximately 75% and near 100%, respectively, at the 20 pmol/L cutoff. A higher sensitivity (>95%) can be achieved using a 5 pmol/L cutoff, and this is the cutoff recommended by the Mayo Clinic’s highly experienced hypoglycemia team to avoid missing cases. However, the lower cutoff results in a reduced specificity (approximately 40%), emphasizing the need for a combination of different tests to assure accurate biochemical diagnosis. Patients with PC1/3 deficiency have low, or sometimes undetectable, insulin levels and substantially elevated proinsulin levels, exceeding the upper limit of the reference range substantially in the fasting state and rising even higher after food intake. Many other hormonal abnormalities are also present, including cortisol deficiency (because of lack of processing of pro-opiomelanocortin to adrenocorticotropic hormone and other peptides), infertility and, often, morbid obesity. This assay demonstrates no cross-reactivity with insulin or C-peptide.

Reference Values:
3-20 pmol/L

libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

**Useful For:** Quantifying prolactin in serum specimens where the high-dose hook effect is suspected (eg, presence of pituitary tumor with symptoms of prolactinoma, and lower than expected serum prolactin concentration)

**Interpretation:** If no high-dose hook effect is observed, the following report comment will be included with the prolactin result: 10-, 100-, and 400-fold dilutions produced results consistent with the absence of high-dose hook effect. Total prolactin was measured using the Roche Cobas e immunoassay analyzer. If a high-dose hook effect is observed, which is demonstrated by significantly increasing concentrations of prolactin obtained after dilution of the serum, an interpretive comment will be included with the prolactin result. The Roche Cobas Prolactin II assay should demonstrate no high-dose hook effect at prolactin concentrations up to approximately 12,500 ng/mL (see Method Description).

**Reference Values:**

- **Males:**
  - <18 years: not established
  - > or =18 years: 4.0-15.2 ng/mL

- **Females:**
  - <18 years: not established
  - > or =18 years: 4.8-23.3 ng/mL

**Clinical References:**

**Prolactin, Serum**

**Clinical Information:** Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and are also elevated during pregnancy, lactation, postpartum, and in the newborn infant. Hyperprolactinemia is the most common hypothalamic-pituitary disorder encountered in clinical endocrinology. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent in females than males, and accounts for approximately 40% of all pituitary tumors), functional and organic disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. Hyperprolactinemia often results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal females, and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

**Useful For:** Aiding in evaluation of pituitary tumors, amenorrhea, galactorrhea, infertility, and
Interpretation: In general, serum prolactin concentrations parallel tumor size in patients with prolactinomas. Macroadenomas (>10 mm in diameter) are typically associated with serum prolactin concentrations >250 ng/mL and a concentration >500 ng/mL is diagnostic of a macroadenoma. Moderately increased concentrations of serum prolactin are not a reliable guide for determining whether a prolactin-producing pituitary adenoma is present. After initiation of medical therapy of prolactinomas, prolactin levels should decrease substantially in most patients; in 60% to 80% of patients, normal levels should be reached. Failure to suppress prolactin levels may indicate tumors resistant to the usual central-acting dopamine agonist therapies; however, a subset of patients will show tumor shrinkage despite persistent hyperprolactinemia. Patients who show neither a decrease in prolactin levels nor tumor shrinkage might require additional therapeutic measures. In patients where a discrepancy between pituitary tumor size and prolactin elevation is observed, a test for false-low serum prolactin (hook effect) should be performed by serial dilution. See PLPMA / Prolactin, Pituitary Macroadenoma. The Roche Cobas Prolactin II assay should demonstrate no high-dose hook effect at prolactin concentrations up to approximately 12,500 ng/mL. (Package insert: Roche E170/Cobas e601/e602 Prolactin II) Multiple medications can cause increased prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide, domperidone), alpha-methyldopa, cimetidine, opiates, antihypertensive medications, and other antidepressants and antipsychotics. In patients with asymptomatic hyperprolactinemia, assessment for macroprolactin (prolactin bound to immunoglobulin) is suggested. Macroprolactin is detected by differing degrees depending on the immunoassay used to measure prolactin. The Roche Cobas Prolactin II assay shows low reactivity with most forms of macroprolactin. (Package insert: Roche E170/Cobas e601/e602 Prolactin II) Macroprolactin should be evaluated in asymptomatic hyperprolactinemic subjects or when pituitary imaging studies are not informative. See MCRPL / Macroprolactin, Serum.

Reference Values:
Males
<18 years: not established
> or =18 years: 4.0-15.2 ng/mL

Females:
<18 years: not established
> or =18 years: 4.8-23.3 ng/mL


PROCT 83097 Prolonged Clot Time Profile

Clinical Information: When coagulation screening tests are performed to verify normal function of the coagulation system (eg, preoperative, routine examination), they sometimes indicate an abnormality that may be unexplained (ie, prolonged clotting times). This consultation provides validation of the prolongation and as comprehensive a work-up as needed to define the abnormality. Possibilities for a cause of prolongation include: -Factor deficiency(ies), congenital or acquired -Factor inhibitors (including Coumadin therapy) -Lupus-like anticoagulant -Heparin contamination -Dilution of specimen by anticoagulant if patient hematocrit is > or =55%

Useful For: Determining cause of prolongation of prothrombin time or activated partial thromboplastin time Screening for prolonged clotting times and determining the presence of factor deficiency(ies) or inhibitor (factor-specific, lupus-like, or the presence of heparin)
**Interpretation:** A interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


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**Prolyl Hydroxylase Domain-2 (PHD2/EGLN1) Gene Sequencing**

**Clinical Information:** Erythrocytosis (increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (polycythemia vera: PV), or secondary, in response to increased erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When extrinsic causes of erythrocytosis are excluded, a heritable cause intrinsic to the RBC or erythrocyte regulatory mechanisms may be suspected. Mutations in genes coding for hemoglobin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate deficiency), the erythropoietin receptor and oxygen-sensing pathway enzymes (hypoxia-inducible factor, prolyl hydroxylase domain, and von Hippel Lindau) can result in erythrocytosis (see Table).

Erythrocytosis Testing Gene Inheritance Serum EPO p50 JAK2V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to Normal Normal PHD2 Dominant Normal Normal BPGM Dominant Normal Decreased Beta Globin Dominant Increased to Normal Decreased Alpha Globin Dominant Increased to Normal Decreased HIF2A Dominant Increased to Normal VHL Recessive Increased Normal The oxygen sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF) that regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO. HIF-alpha is regulated by von Hippel-Lindau (vHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of the serine and histidine residues. Enzymes important in the hydroxylation of HIF are the prolyl hydroxylase domain proteins, which have 3 isoforms-PHD1, PHD2, and PHD3. The most significant isoform associated with erythrocytosis is PHD2. PHD enzymes are oxygen dependent and have an iron-containing active site. Ascorbic acid enhances, but is not essential for, the activity of PHD. Therefore, activity can be modulated by low iron and ascorbic acid levels as well as by low oxygen. Clinically significant PHD2 (official designation EGLN1 [egl nine homolog 1]) mutations are heterozygous and have been found in exons 1 through 4. These mutations result in amino acid substitutions and are associated with inappropriately normal EPO levels.

**Useful For:** Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Interpretation:** Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Reference Values:** Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Clinical References:**

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**Promethazine (Phenergan)**

**Reference Values:**
Reference Range: < 150 ng/mL
### PROMETHEUS FIBROSpec II

**Useful For:** Testing can aid physicians in differentiating no/mild liver fibrosis from moderate to-severe liver fibrosis in patients with hepatitis C, and may help reduce the number of liver biopsies required.

**Reference Values:**
A final report will be attached in MayoAccess.

### PROMETHEUS IBD sgi Diagnostic

**Reference Values:**
Testing is complete. Report has been attached in Mayo Access.

### PROMETHEUS LactoTYPE

**Reference Values:**
A final report will be attached in MayoAccess.

### Prometheus Thiopurine Metabolites

**Reference Values:**
Units of Measure: pmol/8 x 10^8 RBC

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-TGN</td>
<td>230-400</td>
</tr>
<tr>
<td>6-MMPN</td>
<td>&lt;5700</td>
</tr>
</tbody>
</table>

Proprietary and patented technology by Prometheus Laboratories, Inc. The therapeutic range and toxic thresholds were established in an IBD patient population receiving azathioprine or 6-mercaptopurine. Metabolite testing should not replace laboratory monitoring for toxicity.

**Clinical References:**

### Propafenone, Serum

**Clinical Information:** Tocainide, mexiletine, flecainide, and propafenone are all class I antiarrhythmic agents whose dominant cardiac effect is to reduce the rate of rise of the action potential in cardiac cells. In so doing, they increase the threshold of excitability of myocardial cells, depress the
conduction velocity of the impulse around the heart, and prolong the defective refractory period, which results in stabilization of the heart rate. All 4 drugs are effective following oral administration. Tocainide, mexiletine, and flecainide undergo minimal first-pass metabolism and have relatively long half-lives (10-16 hours). In contrast, propafenone undergoes extensive first-pass metabolism (half-life is approximately 1-3 hours). Its clinical efficacy is maintained through the formation of a metabolite (5-hydroxypropafenone) that is more pharmacologically active than the parent drug and has a longer plasma half-life (6-12 hours). Propafenone is primarily used to treat ventricular arrhythmias (ventricular tachycardia, supraventricular tachycardia, and ventricular premature contractions). Specimens should only be drawn after patient has been receiving propafenone orally for at least 3 days. Trough concentrations should be drawn just before administration of the next dose. Adverse side effects are seen in the central nervous system, skin, and gastrointestinal tract.

**Useful For:** Monitoring propafenone therapy

**Interpretation:** The therapeutic concentration is 0.5 to 2.0 mcg/mL; concentrations <0.5 mcg/mL likely indicate inadequate therapy and propafenone >2.0 mcg/mL indicates excessive therapy. Toxic concentration: >2.0 mcg/mL

**Reference Values:**
Therapeutic concentration: 0.5-2.0 mcg/mL

**Clinical References:**

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**FPROP**

90362

**Propofol, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Synonym(s): Diprivan

Patients required a mean blood propofol concentration of 4.05 +/- 1.01 mcg/mL for major surgery and 2.97 +/- 1.07 mcg/mL for non-major surgery. Blood propofol concentrations at which 50% of patients were awake and oriented after surgery were 1.07 and 0.95 mcg/mL respectively.

Psychomotor performance returned to baseline at blood propofol concentrations of 0.38 – 0.43 mcg/mL.

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**FPPOX**

57140

**Propoxyphene (Darvon) and Norpropoxyphene, Serum**

**Reference Values:**
Propoxyphene: 100 â€“ 400 ng/mL
Norpropoxyphene: 200 - 2,200 ng/mL
Propoxyphene + Norpropoxyphene: 400 - 3,000 ng/mL

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**FPRSG**

57149

**Prostaglandin D2 (PG D2), Urine**

**Reference Values:**
100 - 280 ng/24 hrs

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**FPGD2**

90154

**Prostaglandin D2 (PGD2), Serum or Plasma**

**Clinical Information:** Prostaglandins are fatty acids derived from arachidonic acid metabolism. They...
are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2, and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord, intestines, and stomach. Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and Indomethacin.

**Reference Values:**
35 - 115 pg/mL

No pediatric reference ranges available for this test.

This test was performed using a kit that has not been cleared or approved by the FDA and is designated as research use only. The analytic performance characteristics of this test have been determined by Inter Science Institute. This test is not intended for diagnosis or patient management decisions without confirmation by other medically established means.

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**FPGE2**

**Prostaglandin E2 (PG E2), Urine**

**Clinical Information:** Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin E2 is derived mainly from Prostaglandin H2, and is metabolized to Prostaglandin F2a, A2, and Dihydroketo Prostaglandin E2. Prostaglandin E2 is excreted directly into the urine. Prostaglandin E2 is a potent vasodilator and also a stimulus for Renin release. Prostaglandin E2 release is stimulated by cholinergic and alpha adrenergic agents. Prostaglandin E2 potentiates the actions of Histamine and Bradykinin causing pain and accumulation of edema fluid. It relaxes the circular muscle of the gut in opposition to Prostaglandin F2a, and also relaxes the lower esophageal sphincter. Prostaglandin E2 also causes accumulation of water and electrolytes in the lumen of the gut by stimulating their secretion. Elevated levels of Prostaglandin E2 have been detected in patients with the Watery Diarrhea Syndrome, neural crest tumors, pheochromocytomas, and other amine-peptide-secreting tumors. Prostaglandin E2 production and circulating levels are drastically suppressed by aspirin and indomethacin. Urine Prostaglandin E2 levels give an integrated picture of Prostaglandin E2 production over a 24 hour minimizing the effect of diurnal variation and episodic secretion.

**Reference Values:**
400 - 620 ng/24 hours

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**FPSAS**

**Prostate Specific Antigen, Ultrasensitive**

**Clinical Information:** The Roche PSA method is approved for use as an aid in the detection of prostate cancer when used in conjunction with a digital rectal exam in men age 50 and older. The Roche PSA is also indicated for the serial measurement of PSA to aid in the prognosis and management of prostate cancer patients. Elevated PSA concentrations can only suggest the presence of prostate cancer until biopsy is performed. PSA concentrations can also be elevated in benign prostatic hyperplasia or inflammatory conditions of the prostate. PSA is generally not elevated in healthy men or men with nonprostatic carcinoma.

**Interpretation:** After radical prostatectomy, the reference interval is less than 0.05 ng/mL if there is no residual disease. In healthy males without prostatectomy, the reference interval is 4.00 ng/mL or less. Lower limit of detection is 0.01 ng/mL.

**Reference Values:**
0.00 - 4.00 ng/mL
Prostate-Specific Antigen (PSA) Diagnostic, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50, and also for those men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

Useful For: Evaluating patients with documented prostate problems in whom multiple prostate-specific antigen tests may be necessary per year Monitoring patients with a history of prostate cancer as an early indicator of recurrence and response to treatment

Interpretation: Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but further testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values >0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.

Reference Values:

<table>
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<tr>
<th>Age (Years)</th>
<th>PSA Upper Limit (ng/mL)</th>
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<tr>
<td>&lt; or =2.0</td>
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<td>40-49</td>
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<tr>
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<td>&lt; or =7.2 Females: not applicable</td>
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response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50, and also for those men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

**Useful For:** Monitoring patients with a history of prostate cancer as an early indicator of recurrence and response to treatment Prostate cancer screening

**Interpretation:** Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but further testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values >0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.

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**Prostate-Specific Antigen (PSA), Total and Free, Serum**

**Clinical Information:** Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. PSA exists in serum in multiple forms: complexed to alpha-1-anti-chymotrypsin (PSA-ACT complex), unbound (free PSA), and enveloped by alpha-2-macroglobulin (not detected by immunoassays). Higher total PSA levels and lower percentages of free PSA are associated with higher risks of prostate cancer.

**Useful For:** The percentage of measured prostate-specific antigen (PSA) existing in the free form (free:total PSA ratio) is useful in assessing the risk of prostate cancer in patients with borderline or moderately increased total PSA (4.0-10.0 ng/mL) and has been used to help select men who should have follow-up prostate biopsy Most prostate cancers are slow growing, so the utility of prostate cancer screening is marginal in most men with a life expectancy of <10 years.
**Interpretation:** When total prostate-specific antigen (PSA) concentration is <2.0 ng/mL, the probability of prostate cancer in asymptomatic men is low, further testing and free PSA may provide little additional information. When total PSA concentration is >10.0 ng/mL, the probability of cancer is high and prostate biopsy is generally recommended. The total PSA range of 4.0 to 10.0 ng/mL has been described as a diagnostic "gray zone," in which the free:total PSA ratio helps to determine the relative risk of prostate cancer (see table below). Therefore, some urologists recommend using the free:total ratio to help select which men should undergo biopsy. However, even a negative result of prostate biopsy does not rule-out prostate cancer. Up to 20% of men with negative biopsy results have subsequently been found to have cancer. Based on free:total PSA ratio: the percent probability of finding prostate cancer on a needle biopsy by age in years: Free:total PSA ratio 50-59 years 60-69 years > or =70 years < or =0.10 49.2% 57.5% 64.5% 0.11-0.18 26.9% 33.9% 40.8% 0.19-0.25 18.3% 23.9% 29.7% >0.25 9.1% 12.2% 15.8%

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<td>Females: not applicable</td>
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**Prostatic Acid Phosphatase (PAP), Serum**

**Clinical Information:** Prostatic acid phosphatase (PAP), a glycoprotein synthesized by the prostate gland, is a member of a diverse group of isoenzymes, the acid phosphatases, which are capable of hydrolyzing phosphate esters in acidic medium. They are classified on the basis of their electrophoretic mobilities. PAP was a major tumor marker for prostate cancer for more than 50 years. However, PAP is no longer used to screen for or stage prostate cancer. In most instances, serum prostate specific antigen (PSA) is used instead. PAP usefulness is now limited to niche applications. Pre-treatment PAP measurement may add unique, clinically useful prognostic information for predicting recurrence in men who are undergoing radical prostatectomy for clinically localized prostate cancer. PAP also may be useful for following the progression of disease response to therapy in men treated by androgen ablation. However, for both of these applications, PSA provides more information and also should be utilized.

**Useful For:** Predicting recurrence after radical prostatectomy for clinically localized prostate cancer and following response to androgen ablation therapy, when used in conjunction with prostate-specific antigen
**Prostatic acid phosphatase (PAP) levels above the reference range may indicate prostate cancer, but can be due to many other factors, see Cautions. A rise in PAP levels in patients with known prostate cancer can indicate tumor progression or recurrence. However, there is considerable intra-subject biological variability, limiting the usefulness of this test.**

**Reference Values:**
< or =2.1 ng/mL

**Clinical References:**

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**Protein C Activity, Plasma**

**Clinical Information:** Physiology: Protein C is a vitamin K-dependent anticoagulant proenzyme. It is synthesized in the liver and circulates in the plasma. The biological half-life of plasma protein C is approximately 6 to 10 hours, similar to the relatively short half-life of coagulation factor VII. Protein C is activated by thrombin, in the presence of an endothelial cell cofactor (thrombomodulin), to form the active enzyme activated protein C (APC). APC functions as an anticoagulant by proteolytically inactivating the activated forms of coagulation factors V and VIII (factors Va and VIIIa). APC also enhances fibrinolysis by inactivating plasminogen activator inhibitor (PAI-1). Expression of the anticoagulant activity of APC is enhanced by a cofactor, protein S, another vitamin K-dependent plasma protein. Pathophysiology: Congenital homozygous protein C deficiency results in a severe thrombotic diathesis, evident in the neonatal period and resembling purpura fulminans. Congenital heterozygous protein C deficiency may predispose to thrombotic events, primarily venous thromboembolism; arterial thrombosis (stroke, myocardial infarction, etc.) may occur. Some individuals with hereditary heterozygous protein C deficiency may have no personal or family history of thrombosis and may or may not be at increased risk. Congenital heterozygous protein C may predispose to development of coumarin-associated skin necrosis. Skin necrosis has occurred during the initiation of oral anticoagulant therapy. Two types of hereditary heterozygous protein C deficiency are recognized: -Type I (concordantly decreased protein C function and antigen) -Type II (decreased protein C function with normal antigen level) Acquired deficiencies of protein C may occur in association with: -Vitamin K deficiency -Oral anticoagulation with coumarin compounds -Liver disease -Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) The clinical hemostatic significance of acquired protein C deficiency is uncertain. Assay of protein C functional activity is recommended for the initial laboratory evaluation of patients suspected of having congenital protein C deficiency (personal or family history of thrombotic diathesis), rather than assay of protein C antigen (PCAG / Protein C Antigen, Plasma).

**Useful For:** As an initial test for evaluating patients suspected of having congenital protein C deficiency, including those with personal or family histories of thrombotic events Because coagulation testing and its interpretation is complex, Mayo Medical Laboratories suggests ordering THRMP / Thrombophilia Profile. Detecting and confirming congenital Type I and Type II protein C deficiencies, detecting and confirming congenital homozygous protein C deficiency, and identifying decreased functional protein C of acquired origin (eg, due to oral anticoagulant effect, vitamin K deficiency, liver disease, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation.)

**Interpretation:** Values <60% to 70% may represent a congenital deficiency state, if acquired deficiencies can be excluded. Protein C activity (and antigen) is generally undetectable in individuals with severe, homozygous protein C deficiency. Oral anticoagulant therapy (warfarin, Coumadin) decreases protein C activity, compromising the ability to distinguish between congenital and acquired protein C deficiency. Concomitant measurement of the activity of coagulation factor VII (or factor X) may aid in differentiating congenital deficiency state from acquired protein C deficiency due to oral anticoagulant effect, but the ratio of the activities of protein C:factor VII (or factor X) has not been demonstrated to provide certainty about this distinction. The clinical significance of acquired protein C deficiency and of...
increased protein C is unknown.

Reference Values:
Adults: 70%-150%

Normal, full-term newborn infants or healthy premature infants may have decreased levels of protein C activity (15%-50%), which may not reach adult levels until later in childhood or early adolescence.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


PCTR
36878

Protein Catabolic Rate, 24 Hour, Urine

Useful For:

Interpretation:

Reference Values:
Only orderable as part of a profile. For more information see SAT24 / Supersaturation Profile, 24 Hour, Urine.

Clinical References:

SFX
80775

Protein S Activity, Plasma

Clinical Information: Protein S is a vitamin K-dependent plasma glycoprotein synthesized predominantly within the liver. Protein S is also synthesized in endothelial cells and present in platelets. As a part of the plasma anticoagulant system, protein S acts as a necessary cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. About 60% of the total plasma protein S antigen circulates bound to C4b binding protein (C4b-BP), while the remainder circulates as "free" protein S. Only free protein S has anticoagulant activity. Congenital protein S deficiency is an autosomal codominant disorder that is present in 1% to 3% of patients with venous thromboembolism. Heterozygous protein S deficiency carriers have approximately a 10-fold increased risk of venous thromboembolism. Other phenotypic expressions of heterozygous congenital protein S deficiency include recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of heterozygous congenital protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S (APC cofactor) activity in plasma. Types of Heterozygous Protein S Deficiency Type Protein S Antigen, Free Protein S Antigen, Total Protein Activity I Decreased Decreased Decreased II Normal Normal Decreased III Decreased Normal Decreased Type I and III protein S deficiency are much more common than Type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4b-BP. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) caused by the absence or near absence of plasma protein S. Acquired deficiency of protein S is much more common than hereditary protein S deficiency and is generally of unknown hemostatic significance (ie, uncertain thrombosis risk). Among the many causes of acquired protein S deficiency are: -Vitamin K deficiency -Oral anticoagulant therapy -Acute illness (eg, acute thrombosis, recent surgery, or other disorder associated with acute inflammation) -Liver disease -ICF/DIC -Thrombotic thrombocytopenic purpura -Pregnancy, oral contraceptive, or estrogen therapy -Nephrotic syndrome -Sickle cell anemia

Useful For: Second-order testing for diagnosis of congenital or acquired protein S deficiency for example, as an adjunct to initial testing based on results of protein S antigen assay (free protein S antigen, with or without total protein S antigen assay) Evaluating patients with a history of venous thromboembolism
**Interpretation:** In Type I and Type III congenital deficiency, free protein S antigen is decreased and protein S functional activity is similarly decreased. In Type II congenital (dysfunctional) protein S deficiency, total and free protein S antigen levels are normal but functional activity is decreased. Patients with acquired free protein S deficiency associated with inflammation-related increase of C4b-BP typically have decreased free protein S antigen (and protein S activity) and normal (or elevated) total protein S antigen. Acquired protein S deficiency is of uncertain clinical hemostatic significance and is associated with a variety of conditions. Elevated protein S levels are of uncertain clinical significance.

**Reference Values:**
Males: 65-160%
Females
<50 years: 50-160%
> or =50 years: 65-160%
Newborn infants have normal or near-normal free protein S antigen (> or =50%), although total protein S antigen is usually below the adult reference range. There are insufficient data concerning protein S activity in normal neonates, infants, and children; but normal or near-normal activity (> or =50%) probably is present by age 3 to 6 months.

**Clinical References:**

**Protein S Antigen, Plasma**

**Clinical Information:** Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the complement regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP while the remaining 40% circulates as “free” protein S. Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown haemostatic significance (ie, uncertain thrombosis risk), and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy or
estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

**Useful For:** Investigation of patients with a history of thrombosis

**Interpretation:** Protein S values vary widely in the normal population and are age- and sex-dependent. Types of Heterozygous Protein S Deficiency Type Protein S Antigen Free Protein S Antigen Total Protein S Activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4bBP are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, S_FX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful, but is generally not yet available.

**Reference Values:**

**TOTAL**
- Males: 80-160%
- Females
  - <50 years: 70-160%
  - > or =50 years: 80-160%

**FREE**
- Males: 65-160%
- Females
  - <50 years: 50-160%
  - > or =50 years: 65-160%

Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15-50%); but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (> or =50%). Total protein S reaches adult levels by 90 to 180 days postnatal.*

**Clinical References:**

Protein, Total, 12 Hour, Urine

Clinical Information: Protein in urine normally consists of plasma proteins that have been filtered by glomeruli and not reabsorbed by the proximal tubule, and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: increased plasma concentration of proteins that exceeds capacity for proximal tubular reabsorption (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor -Preeclampsia -Orthostatic proteinuria In pregnant women, a urinary protein excretion of >300 mg/24 hours is frequently cited as consistent with preeclampsia, and 12-hour total protein excretion highly correlates with 24-hour values in this patient population.(1,2) Orthostatic proteinuria is characterized by increased protein excretion in the upright position, but normal levels when supine. This condition can be detected by comparing urine protein levels in a collection split between day and night (see OPTU / Orthostatic Protein, Timed Collection, Urine). Orthostatic proteinuria is common in childhood and adolescence, but rare after age 30.

Useful For: Evaluation of renal disease Screening for monoclonal gammopathy Screening for postural (orthostatic) proteinuria In select clinical situations, collection of a 12-hour specimen may allow more rapid detection of proteinuria states (eg, screening pregnant patients for preeclampsia)

Interpretation: Total urine protein determined to be >500 mg/24 hours should be evaluated by immunofixation to assess if there is a monoclonal immunoglobulin light chain and, if present, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

Reference Values:
<115 mg/12 hours (day or night collection) Reference values have not been established for patients <18 years of age. Reference values have not been established for patients >83 years of age.


Protein, Total, 24 Hour, Urine

Clinical Information: Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins(s) (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor
Useful For: Evaluation of renal disease Screening for monoclonal gammopathy

Interpretation: Total protein >500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present, and if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

Reference Values:
<167 mg/24 hours
Reference values have not been established for patients <18 years of age.
Reference values have not been established for patients >83 years of age.
Reference value applies to 24-hour collection.


TPBF 8420
Protein, Total, Body Fluid

Clinical Information: Not available

Useful For: Not established

Interpretation: None available

Reference Values: Not applicable


RPTU 85681
Protein, Total, Random, Urine

Clinical Information: Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinuria)

Useful For: Evaluation of renal disease Screening for monoclonal gammopathy

Interpretation: Total protein >500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present, and if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract. In a random urine specimen, a protein/creatinine or protein/osmolality ratio can be used to roughly approximate 24-hour excretion rates. The normal protein-to-creatinine ratio for males 18 to 83 years is <0.11 mg/mg creatinine and for females 18 to 83 years is <0.16 mg/mg creatinine. The normal protein-to-osmolality ratio is <0.27.(1) For patients <18 years of age and >83 years of age no reference range has been established.

Reference Values:
Males <0.11 mg/mg creatinine
Reference values have not been established for male patients <18 years of age.
Reference values have not been established for male patients >83 years of age.

Females <0.16 mg/mg creatinine
Reference values have not been established for female patients <18 years of age. Reference values have not been established for female patients >83 years of age.

**Clinical References:**

**Protein, Total, Serum**

**Clinical Information:** Plasma proteins are synthesized predominantly in the liver; immunoglobulins are synthesized by mononuclear cells of lymph nodes, spleen and bone marrow. The 2 general causes of alterations of serum total protein are a change in the volume of plasma water and a change in the concentration of one or more of the specific proteins in the plasma. Of the individual serum proteins, albumin is present in such high concentrations that low levels of this protein alone may cause hypoproteinemia. Hemoconcentration (decrease in the volume of plasma water) results in relative hyperproteinemia; hemodilution results in relative hypoproteinemia. In both situations, concentrations of all the individual plasma proteins are affected to the same degree. Hyperproteinemia may be seen in dehydration due to inadequate water intake or to excessive water loss (eg, severe vomiting, diarrhea, Addison's disease and diabetic acidosis) or as a result of increased production of proteins. Increased polyclonal protein production is seen in reactive, inflammatory processes; increased monoclonal protein production is seen in some hematopoietic neoplasms (eg, multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of undetermined significance).

**Useful For:** Diagnosis and treatment of a variety of diseases involving the liver, kidney, or bone marrow, as well as other metabolic or nutritional disorders

**Interpretation:** Mild hyperproteinemia may be caused by an increase in the concentration of specific proteins normally present in relatively low concentration, eg, increases in acute phase reactants and polyclonal immunoglobulins produced in inflammatory states, late-stage liver disease, and infections. Moderate-to-marked hyperproteinemia may also be due to multiple myeloma and other malignant paraproteinemias, although normal total protein levels do not rule out these disorders. A serum protein electrophoresis should be performed to evaluate the cause of the elevated serum total protein. Hypoproteinemia may be due to decreased production (eg, hypogammaglobulinemia) or increased protein loss (eg, nephrotic syndrome, protein-losing enteropathy). A serum protein electrophoresis should be performed to evaluate the cause of the decreased serum total protein. If a nephrotic pattern is identified, urine protein electrophoresis should also be performed.

**Reference Values:**
> or =1 year: 6.3-7.9 g/dL

Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

**Protein, Total, Spinal Fluid**

**Clinical Information:** Cerebrospinal fluid (CSF) is secreted by the choroid plexuses, around the cerebral vessels, and along the walls of the ventricles of the brain. It fills the ventricles and cisternae, bathes the spinal cord, and is reabsorbed into the blood through the arachnoid villi. CSF turnover is rapid, exchanging about four times per day. More than 80% of CSF protein content originates from plasma by ultrafiltration through the walls of capillaries in the meninges and choroid plexuses; the remainder originates from intrathecal synthesis. Because CSF is mainly an ultrafiltrate of plasma, low-molecular
plasma proteins such as prealbumin, albumin, and transferrin predominate. No protein with a molecular weight greater than that of IgG is present in sufficient concentration to be visible on electrophoresis. The permeability of the blood-brain barrier to plasma proteins is increased by high intracranial pressure due to brain tumor; intracerebral hemorrhage; traumatic injury; or by inflammation due to bacterial or viral meningitis, encephalitis, or polyomylitis. Increased intrathecal synthesis of immunoglobulins, particularly IgG, is seen in demyelinating diseases of the central nervous system (CNS), especially multiple sclerosis. Increased immunoglobulins are also seen in other chronic inflammatory diseases of the CNS such as chronic meningoencephalitis due to bacteria, viruses, fungi or parasites; subacute sclerosing panencephalitis; and Guillian-Barre syndrome.

**Useful For:** To detect increased permeability of the blood-brain barrier to plasma proteins To detect increased intrathecal production of immunoglobulins

**Interpretation:** Striking elevations of cerebrospinal fluid (CSF) total protein are noted in bacterial meningitis; smaller elevations occur in the other inflammatory diseases and with tumor or hemorrhage. The effect of any of these conditions is that the proportions of specific proteins in CSF increasingly resemble serum. In order to assess increased permeability or increased intrathecal production of proteins, simultaneous serum specimen and CSF specimens should be taken.

**Reference Values:**
> or =12 months: 0-35 mg/dL

Reference values have not been established for patients that are <12 months of age.


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**Proteinase 3 Antibodies, IgG, Serum**

**Clinical Information:** Proteinase 3 (PR3) antigen is a 29kD serine protease that exists as a protein triplet in human neutrophils. Wegener granulomatosis (WG) is an autoimmune vasculitis that affects the kidneys and lungs, as well as other organs. Patients with WG develop autoantibodies to the PR3 antigen of myeloid lysosomes (PR3 antineutrophil cytoplasmic antibodies [PR3 ANCA]).(1) Since it is often impossible to distinguish between WG and other forms of vasculitis on the basis of clinical signs and symptoms, tests for PR3 ANCA should be employed with other serologic tests in the initial diagnostic evaluation of patients with clinical features of vasculitis (eg, VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum).

**Useful For:** Evaluating patients suspected of having Wegener granulomatosis (WG) Distinguishing between WG and other forms of vasculitis, in conjunction with MPO / Myeloperoxidase Antibodies, IgG, Serum and ANCA / Cytoplasmic Neutrophil Antibodies, Serum (may be obtained as VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum) May be useful to follow treatment response or to monitor disease activity in patients with myeloperoxidase antibodies

**Interpretation:** Proteinase 3 antineutrophil cytoplasmic antibodies (PR3 ANCA) are detectable in nearly all patients with severe active Wegener granulomatosis (WG).(2) The presence of PR3 ANCA is a specific diagnostic indicator of WG; <2% of positive results occur in patients who do not have the disease.(3,4) A negative result for PR3 ANCA diminishes the likelihood that a patient has active WG; but, approximately 20% of patients with limited WG may test negative for PR3 ANCA.(3) The levels of PR3 ANCA often decline following successful treatment of patients with WG. Nevertheless, follow-up testing for PR3 ANCA to evaluate clinical status in treated patients should be used with caution as the levels of antibodies may correlate poorly with clinical status in some patients.

**Reference Values:**
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)

Reference values apply to all ages.

Prothrombin Fragment 1+2
Reference Values:
87 - 325 pmol/L

Pre-analytical conditions such as a difficult draw may spuriously increase test results.

Prothrombin G20210A Mutation, Blood
Clinical Information: Venous thromboembolism (VTE) is a syndrome of deep vein thrombosis and its complication, pulmonary embolism. The prothrombin (PT) G20210A mutation (F2 rs1799963) is a common polymorphism within the 3' untranslated region of the prothrombin gene, affecting 1.5% to 3% of Caucasian Americans, especially persons of southern European ancestry. The PT G20210A allele is uncommon among African Americans (carrier frequency of 0.4%). The PT G20210A mutation is associated with a 3-fold increased risk of venous thromboembolism due to increased plasma prothrombin activity among carriers. The PT G20210A gene mutation test is a direct mutation analysis of patient blood leukocyte genomic DNA. At present, there are no other methods of detecting this VTE risk factor except for direct mutation testing.

Useful For: Direct mutation analysis for the prothrombin (PT) G20210A allele should be reserved for patients with clinically suspected thrombophilia. There may be additional indications for direct PT G20210A mutation testing, such as in determining the duration of anticoagulation therapy of venous thromboembolism patients and screening for women contemplating hormone therapy.

Interpretation: The interpretive report will include sample information, assay information, background information, and conclusions drawn from the test results (normal, heterozygous prothrombin [PT] G20210A, homozygous PT G20210A).

Reference Values:
Negative


Prothrombin Time, Plasma

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1647
Clinical Information: The prothrombin time (PT) represents the time elapsed between: 1) addition of a standardized mixture of tissue thromboplastin and calcium to citrate anticoagulated plasma and; 2) detection of clot formation, representing fibrin polymerization resulting from the generation of thrombin, which proteolytically transforms fibrinogen to fibrin. Tissue thromboplastin is a mixture of phospholipid vesicles and tissue factor (TF), a protein cofactor. Tissue thromboplastins have traditionally been prepared from animal tissue extracts (brain, placenta, lung) however, the recent availability of recombinantly derived human TF combined with purified phospholipid mixtures allows preparation of well-defined tissue thromboplastin with several potential advantages. Together with phospholipid, TF forms a complex with coagulation factor VII/VIIa (activated factor VII), providing an enzyme-cofactor complex which, in the presence of ionic calcium, activates proenzyme coagulation factor X to the enzyme factor Xa. Factor Xa, in turn, forms a complex with phospholipid, calcium, and activated factor V (Va, a protein cofactor) to form prothrombinase, which hydrolyzes factor II substrate (prothrombin) to the active coagulant enzyme thrombin. Thrombin hydrolyzes fibrinogen (factor I) by cleaving specific peptides (fibrinopeptides A and B), to form fibrin monomer, which assembles into fibrin polymers (a clot). The PT is not sensitive to deficiencies of coagulation factors VIII, IX, XI, XII ("intrinsic pathway" factors), or factor XIII, although the TF/VIIa complex can activate factor IX (in addition to factor X). A prolonged PT indicates deficiency of 1 or more coagulation factors (I, II, V, VII, or X) or the presence of a coagulation inhibitor. The PT is the most common test used for monitoring oral anticoagulant therapy (warfarin or Coumadin, and congeners). Oral anticoagulants reduce the activities of the 4 vitamin K-dependent procoagulant factors (factors II, VII, IX, and X), and the PT is sensitive to 3 of them. The PT requires standardization because there are numerous thromboplastins and coagulation testing instruments, and they all vary in their responsiveness to the concentrations or activities of coagulation proteins. The international normalized ratio (INR) is a method of standardizing PT reporting for monitoring the intensity of oral anticoagulant therapy. The INR is the ratio of the patient’s PT to the laboratory’s mean normal (reference) PT. The international sensitivity index (ISI) is an experimentally derived measurement, usually provided by the thromboplastin manufacturer, reflecting thromboplastin (and PT) sensitivity to coagulation deficiencies. More sensitive thromboplastins have a low ISI (1.0-1.2), whereas less sensitive thromboplastins have a higher ISI (eg, 2.0-3.0). Calculation of the INR is as follows: INR = (Patient’s PT/mean PT of reference range) ISI where: -INR=international normalized ratio -ISI=international sensitivity index Recommended INR therapeutic ranges for orally administered drugs are as follows: -Anticoagulation intensity: INR -Standard intensity: 2.0 to 3.0 -Higher intensity: 3.0 to 4.5 The INR is used only for patients on stable oral anticoagulant therapy. It makes no significant contribution to the diagnosis or treatment of patients whose PT is prolonged for other reasons. At Mayo Clinic and for Mayo Medical Laboratories clients, the PT test is performed with a sensitive thromboplastin (ISI 1.0 +/- 0.05), containing phospholipid and recombinantly derived TF.

Useful For: Monitoring intensity of oral anticoagulant therapy when combined with INR reporting Screening assay to detect deficiencies of 1 or more coagulation factors (factors I, II, V, VII, X) due to: -Hereditary or acquired deficiency states -Vitamin K deficiency -Liver disease -Specific coagulation factor inhibitors Screening assay to detect coagulation inhibition ("circulating anticoagulants") associated with: -Specific coagulation factor inhibitors -Lupuslike anticoagulant inhibitors (antiphospholipid antibodies) -Nonspecific prothrombin time inhibitors (eg, monoclonal immunoglobulins, elevated fibrin degradation products)

Interpretation: The prothrombin time (PT) test varies in its sensitivity to the activity of coagulation factors II, V, VII, and X, and is least sensitive to decreased factor II. Mixing studies with normal plasma (ie, adding various proportions of normal pooled plasma to patient plasma) are useful in initial evaluation of prolonged PT when the cause of a prolonged PT is unknown (eg, not attributable to known oral anticoagulation or known coagulation factor deficiency): -Typically an equal volume mixture (1:1) of patient and normal plasma shortens the prolonged PT into the normal (reference) range when there is a deficiency of 1 or more of the clotting factors (I, II, V, VII, X). Failure to normalize the PT in 1:1 mixing suggests presence of an inhibitor (eg, specific factor inhibitor, lupuslike anticoagulant or antiphospholipid antibody, nonspecific inhibitor). -Typically the addition of patient plasma of 1/10 or 2/10 volume of normal plasma shortens the prolonged PT, at least halfway toward the upper normal range, when there is a deficiency of 1 or more relevant coagulation factors. Inhibition is implied by failure to significantly shorten the PT. -Additional coagulation testing may be needed to define the cause of an unexplained prolonged PT (eg, other clotting time tests, coagulation factor assays, testing for presence of a lupuslike anticoagulant). Mixing studies and such additional testing may be included in consultative testing.
Reference Values:
PROTHROMBIN TIME
9.5-13.8 seconds

INTERNATIONAL NORMALIZED RATIO (INR)
0.8-1.2
The INR is used only for patients on stable oral anticoagulant therapy. It makes no significant contribution to the diagnosis or treatment of patients whose PT is prolonged for other reasons.

PPFWE 31891

Protoporphyrins, Fractionation, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by diminished ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin in plasma and feces. Other possible cases of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies. There are 2 test options: PPFE / Protoporphyrins, Fractionation, Whole Blood and PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Preferred test for analysis of erythrocyte protoporphyrin fractions Preferred test for evaluating patients with possible diagnoses of erythropoietic protoporphyria and X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria, and X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
FREE PROTOPORPHYRIN
<20 mcg/dL packed cells

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL packed cells
**Clinical References:**

**Protoporphyrins, Fractionation, Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease.

EPP is caused by diminished ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin in erythrocytes, and total protoporphyrin levels in plasma and feces. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies. There are 2 test options: PPFE / Protoporphyrins, Fractionation, Whole Blood and PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Evaluating patients with possible diagnoses of erythropoietic protoporphyria or X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
FREE PROTOPORPHYRIN
<20 mcg/dL packed cells

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL packed cells


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**PROTR**

**9797**

**Protriptyline (Vivactyl)**

**Reference Values:**

Reference Range: 50 - 170 ng/mL

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**PRSSZ**

**35532**

**PRSS1 Gene, Full Gene Analysis**

**Clinical Information:** Hereditary pancreatitis (HP) is a rare autosomal dominant disorder associated with approximately 80% penetrance. HP is characterized by early onset acute pancreatitis during childhood or early adolescence. The acute pancreatitis in these patients generally progresses to chronic pancreatitis by adulthood and can eventually lead to both exocrine and endocrine pancreatic insufficiency. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%. Mutations in the protease serine 1 or cationic trypsinogen (PRSS1) gene are a common cause of HP. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis. PRSS1 mutations are infrequently found in patients with alcohol-induced and tropical pancreatitis. Although several mutations have been identified, the R122H, N29I and A16V mutations are the most common disease-causing mutations associated with HP. Data suggest that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Although these 3 alterations account for >90% of mutations detected in the cationic trypsinogen gene, the inability to identify mutations in approximately 20% of families with HP suggests the involvement of other loci or unidentified mutations in the cationic trypsinogen gene. Mutations in other genes, such as SPINK1, CFTR and CTRC have been associated with hereditary and familial pancreatitis. Abnormalities in these genes are not detected by this assay. However, genetic testing for these genes simultaneously, including PRSS1, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

**Useful For:** Confirmation of suspected clinical diagnosis of hereditary pancreatitis (HP) in patients with chronic pancreatitis Identification of familial PRSSI mutation to allow for predictive and diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

An interpretive report will be provided.

Pseudocholinesterase, Dibucaine Inhibition, Serum

Clinical Information: Serum cholinesterase, often called pseudocholinesterase (PCHE), is distinguished from acetylcholinesterase or "true cholinesterase," by both location and substrate. Acetylcholinesterase is found in erythrocytes, in the lungs and spleen, in nerve endings, and in the gray matter of the brain. It is responsible for the hydrolysis of acetylcholine released at the nerve endings to mediate transmission of the neural impulse across the synapse. PCHE, the serum enzyme, is also found in liver, pancreas, heart, and white matter. Its biological role is unknown. The organophosphorus-containing insecticides are potent inhibitors of the true cholinesterase and cause depression of PCHE. Low values of PCHE are also found in patients with liver disease. In general, patients with acute hepatitis and chronic hepatitis of long duration will show a 30% to 50% decrease in PCHE values, while patients with advanced cirrhosis and carcinoma with metastases will show a 50% to 70% decrease. Essentially normal values are seen in chronic hepatitis, mild cirrhosis, and obstructive jaundice. PCHE metabolizes the muscle relaxants succinylcholine and mivacurium, and therefore, alterations in PCHE will influence the physiologic effect of these drugs. In normal individuals (approximately 94% of the population) certain drugs and other agents, such as dibucaine and fluoride, will almost completely inhibit the PCHE activity. A small number of patients (<1% of the population) are homozygous for an atypical gene controlling PCHE. These individuals generally have low levels of PCHE which are not inhibited by dibucaine and fluoride, will not hydrolyze the drugs succinylcholine and mivacurium rapidly enough, and may enter a period of prolonged apnea. In addition to fluoride and dibucaine alleles, a "silent gene" has also been identified which shows little or no activity. More recently, the J and K variants also have been identified. All combinations of heterozygotes of the various alleles have been found. This is important because these atypical enzymes will show varying levels of enzyme activity and resistance to dibucaine although the patients clinically show prolonged apnea.

Useful For: Identifying patients who are homozygous for the atypical gene, and have low levels of pseudocholinesterase (PCHE) which are not inhibited by dibucaine Identifying patients who are heterozygous for the atypical gene, have lower than normal levels of PCHE and varying levels of inhibition with dibucaine

Interpretation: Patients with normal pseudocholinesterase (PCHE) activity show 70% to 90% inhibition by dibucaine, while patients homozygous for the abnormal allele show little or no inhibition (0%-20%) and usually low levels of enzyme. Heterozygous patients have intermediate PCHE levels and response to inhibitors. The atypical gene is inherited in an autosomal recessive pattern. In a positive patient, family members should be tested. Several reports have shown that 65% to 75% of patients who respond abnormally to succinylcholine had at least 1 abnormal gene, had low activity due to an acquired deficiency such as liver disease, or had received an inappropriate dose of drug. The remaining 25% to 35% of patients appeared to have the usual or normal genotype but nevertheless displayed long periods of apnea. Although reasons could not be established, it is possible that these cases represent unknown genotypes. Therefore, although many symptomatic patients will show moderate to significant resistance to dibucaine and low enzyme activity, not all will. In all cases, it is recommended that succinylcholine and mivacurium be avoided, or the dose greatly reduced.

Reference Values:
DIBUCAINE INHIBITION
70-90%
Congenital deficiency: 18-20%

PSEUDOCHOLINESTERASE, TOTAL
Pseudocholinesterase, Total, Serum

Clinical Information: Serum cholinesterase, often called pseudocholinesterase (PCHE), is distinguished from acetylcholinesterase or "true cholinesterase," by both location and substrate. Acetylcholinesterase is found in erythrocytes, in the lungs and spleen, in nerve endings, and in the gray matter of the brain. It is responsible for the hydrolysis of acetylcholine released at the nerve endings to mediate transmission of the neural impulse across the synapse. PCHE, the serum enzyme, is also found in liver, pancreas, heart, and white matter. Its biological role is unknown. The organophosphorus-containing insecticides are potent inhibitors of the true cholinesterase and also cause depression of PCHE. Low values of PCHE are also found in patients with liver disease. In general, patients with advanced cirrhosis and carcinoma with metastases will show a 50% to 70% decrease. Essentially normal values are seen in chronic hepatitis, mild cirrhosis, and obstructive jaundice. PCHE metabolizes the muscle relaxants succinylcholine and mivacurium, and therefore, alterations in PCHE will influence the physiologic effect of these drugs. In normal individuals (approximately 94% of the population) certain drugs and other agents, such as dibucaine and fluoride, will almost completely inhibit the PCHE activity. A small number of individuals (<1% of the population) have been shown to have genetic variants of the enzyme, and cannot metabolize the muscle relaxants succinylcholine and mivacurium and experience prolonged apnea. These individuals generally have low levels of PCHE, which is not inhibited by dibucaine or fluoride. These individuals are either homozygotes or compound heterozygotes for an atypical gene(s) controlling PCHE. Simple heterozygotes have also been identified who show intermediate enzyme values and inhibition.

Useful For: Monitoring exposure to organophosphorus insecticides Monitoring patients with liver disease, particularly those undergoing liver transplantation Identifying patients who are homozygous or heterozygous for an atypical gene and have low levels of pseudocholinesterase

Interpretation: Patients with normal pseudocholinesterase (PCHE) activity show 70% to 90% inhibition by dibucaine, while patients homozygous for the abnormal allele show little or no inhibition (0%-20%) and usually low levels of enzyme. Heterozygous patients have intermediate PCHE levels and response to inhibitors. The atypical gene is inherited in an autosomal recessive pattern. In a positive patient, family members should be tested. Decreasing or low levels may indicate exposure to organophosphorus insecticides, as long as liver disease and an abnormal allele have been ruled out.

Reference Values:
Males
> or =18 years: 3,100-6,500 U/L
Females
18-49 years: 1,800-6,600 U/L
> or =50 years: 2,550-6,800 U/L
Reference values have not been established for patients that are <18 years of age.

Psychosine, Blood Spot

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by an enzyme deficiency of galactocerebrosidase (GALC). Krabbe disease is caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Eighty-five to ninety percent of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. Ten to 15 percent of individuals have late onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anytime from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Treatment is mostly supportive, although hematopoietic stem cell transplantation has shown some success if treatment begins before neurologic damage has occurred. Psychosine (PSY), a neurotoxin at elevated concentrations, is 1 of 4 substrates degraded by galactocerebrosidase. It has been shown to be elevated in patients with active disease and therefore, may be a useful biomarker for the presence of disease or disease progression. PSY measurement in dried blood spots is under study to determine if it is a useful follow-up to an abnormal newborn screen for Krabbe disease. Reduced or absent galactocerebrosidase in leukocytes (CBGC / Galactocerebrosidase, Leukocytes) or fibroblasts (CBGT / Galactocerebrosidase, Fibroblasts) along with psychosine analysis can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) allows for detection of the disease-causing mutations in affected patients and carrier detection in family members.

Useful For: Quantification of psychosine (galactosylsphingosine) in dried blood spots to support the biochemical diagnosis and follow-up of individuals affected with Krabbe disease

Interpretation: An elevation of psychosine is indicative of Krabbe disease.

Reference Values:
Normal <10 nmol/L psychosine


PTEN Gene, Full Gene Analysis

Clinical Information: Germline mutations in the PTEN gene are associated with a rare collection of clinical syndromes referred to as PTEN hamartoma tumor syndrome (PHTS). This includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS) and Proteus-like syndrome (PLS). Although each of these syndromes has its own unique features, all 4 appear to be associated with multiple hamartomatous lesions, vascular lesions, and macrocephaly. Affected individuals have an increased risk of cancer, including cancers of the breast, endometrium, thyroid, colon, and kidney. PHTS is an autosomal dominant disorder and penetrance is believed to be quite high. CS is a multiple hamartoma syndrome associated with trichilemmomas, mucocutaneous papillomatous papules, and macrocephaly. Affected individuals are at an increased risk for breast, thyroid, and endometrial carcinoma. BRRS is characterized by macrocephaly, intestinal hamartomas, lipomatosis, hemangiomas, and pigmented macules on the glans penis. PS is associated with congenital malformations, overgrowth, macrocephaly, hyperostosis, connective tissue nevi, and epidermal nevi. PLS...
refers to individuals who have features of PS, but do not meet diagnostic criteria.

**Useful For:** Confirming a diagnosis of PTEN hamartoma tumor syndrome, which includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, or Proteus-like syndrome

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FPTHC**

**PTH Accuratio Comprehensive Profile**

**Reference Values:**

**COMPREHENSIVE PROFILE**

- TOTAL PTH Reference Range: 14.0 - 66.0 pg/mL
- CAP PTH Reference Range: 5.0 - 39.0 pg/mL
- CIP VALUE Reference Range: 2.5 - 29.0 pg/mL
- CAP/CIP Reference Range: 1.1 - 6.9 ratio

Low ratio or PTH values are associated with Adynamic bone turnover status for an ESRD patient.

**Total PTH:**
Total Intact PTH is the sum of CAP PTH and N-truncated PTH fragment (likely 7-84) Total PTH = Intact PTH = CAP + CIP.

FDA approved.

**CAP PTH:**
CAP stands for Cyclase Activating PTH and is the same as Whole PTH which is 1-84 PTH and which raises bone turnover.

FDA approved.

**CIP VALUE:**
CIP stands for Cyclase Inactive PTH and the N-truncated PTH fragment, likely 7-84 PTH. CIP = Total PTH â€“ CAP.

**CAP/CIP:**
CAP/CIP ratio is a calculated value and has been shown to be 93% predictive of bone turnover for the ESRD patient, however, bone biopsy is 100% predictive, therefore, clinical correlation is recommended.

Reference ranges were established using a 95% reference interval on a normal population with normal functioning kidneys. These reference ranges should not be applied to ESRD patients with impaired or...
non-functioning renal function.


### **FPTH**

**90182 PTH Antibody**

**Reference Values:**

Negative

### **PT1K**

**89464 PTPN11 Gene, Known Mutation, Blood**

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be underestimated. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and multiple lentigines (LEOPARD: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of Noonan syndrome and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-MAPK pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 approximately 10%, and KRAS less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in up to 30% to 75% of families. The PTPN11 gene comprises 15 exons and encodes the Src homology-2 domain-containing phosphatase (SHP-2), a widely expressed extracellular protein. SHP-2 is a key molecule in the cellular response to growth factors, hormones, cytokines, and cell adhesion molecules. It is required in several intracellular signal transduction pathways that control diverse developmental processes. Most reported mutations in PTPN11 are missense mutations, although small deletions as well as whole gene duplications have been reported to cause NS. Most mutations associated with NS destabilize the catalytically inactive conformation of the protein, causing a gain of function of SHP-2. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 mutations are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy (HCM) is commonly associated with RAF1 mutations but rarely associated with PTPN11. Mutations in PTPN11 have also been identified in individuals with a variety of other disorders that overlap phenotypically with NS. PTPN11 has been associated with LEOPARD syndrome, an autosomal dominant disorder sharing several clinical features with NS and characterized by multiple lentigines and cafe-au-lait spots, facial anomalies, and cardiac defects. Two mutations, p.Tyr279Cys and p.Thr468Met, represent the most common PTPN11 mutations found in LEOPARD syndrome, although other mutations have been described. Mutations in PTPN11 have also been identified in patients who have clinical features of NS along with features of CFC syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial
features, and severe psychomotor developmental delay. Genetic testing for PTPN11 mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Genetic testing of individuals at risk for a known PTPN11

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

PTPN11, Full Gene Sequence, Blood

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be underestimated. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-MAPK pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals with NS. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 approximately 10%, and KRAS less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in 30% to 75% of families. The PTPN11 gene comprises 15 exons and encodes the Src homology-2 domain-containing phosphatase (SHP-2), a widely expressed extra-cellular protein. SHP-2 is a key molecule in the cellular response to growth factors, hormones, cytokines, and cell adhesion molecules. It is required in several intracellular signal transduction pathways that control diverse developmental processes. Most reported mutations in PTPN11 are missense mutations, although small deletions as well as whole gene duplications have been reported to cause NS. Most mutations associated with NS destabilize the catalytically inactive conformation of the protein, causing a gain of function of SHP-2. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 mutations are more likely to be found when pulmonary stenosis is present, while hypertrophic...
cardiomyopathy (HCM) is commonly associated with RAF1 mutations, but rarely associated with PTPN11. Mutations in PTPN11 have also been identified in individuals with a variety of other disorders that overlap phenotypically with NS. PTPN11 has been associated with LEOPARD syndrome, an autosomal dominant disorder sharing several clinical features with NS and characterized by multiple lentigines and cafe-au-lait spots, facial anomalies, and cardiac defects. Two mutations, p.Tyr279Cys and p.Thr468Met, represent the most common PTPN11 mutations found in LEOPARD syndrome, although other mutations have been described. Mutations in PTPN11 have also been identified in patients who have clinical features of NS along with features of CFC syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Genetic testing for PTPN11 mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Aiding in the diagnosis of PTPN11-associated Noonan syndrome and LEOPARD syndrome

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


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**PTP22 Genotype, 1858C->T**

**Clinical Information:** Rheumatoid arthritis (RA) is a systemic autoimmune disease that is characterized by joint inflammation and destruction. It is heterogeneous, with genetic and environmental factors contributing to its development.(1) There is a well-established link between an increased risk of developing RA and specific alleles of the human leukocyte antigen (HLA) complex including HLA-DRB1*0404, HLA-DRB1*0405, and HLA-DRB1*0101. It has been estimated that those HLA alleles are responsible for approximately 50% of the genetic susceptibility to RA.(1) Recently, other genes have been identified that also influence the susceptibility of an individual to developing RA. The gene PTPN22 (protein tyrosine phosphatase, non-receptor type 22) encodes the protein Lyp, a phosphatase that is responsible, in part, for regulating T-cell activation. A particular single nucleotide polymorphism (SNP) in PTPN22, designated as 1858C->T, is found more frequently in individuals with autoimmune diseases, including RA, than in healthy control cohorts.(2) It has been proposed that the 1858C->T SNP alters the function of the Lyp, rendering the individual more susceptible to developing RA.(2) In addition, in patients diagnosed with RA, the presence of the T allele has been linked to certain disease phenotypes, including positivity for cyclic citrullinated peptide (CCP) antibodies (a marker for RA), earlier age at diagnosis, and increased rate of joint erosion.(3)

**Useful For:** Identifying individuals previously diagnosed with rheumatoid arthritis who may be at increased risk for developing more severe, erosive articular disease

**Interpretation:** In individuals with rheumatoid arthritis, the presence of the T allele, either as a C/T heterozygote or as a T/T homozygote, suggests an increased risk for the development of more severe
articular disease. Individuals who are homozygous for the C allele (C/C) may have a less aggressive disease course.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Pumpkin Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Purine and Pyrimidine Panel, Urine

Clinical Information: Purines (adenine, guanine, xanthine, hypoxanthine) and pyrimidines (uracil, thymine, cytosine, orotic acid) are involved in all biological processes, providing the basis for storage, transcription, and translation of genetic information as RNA and DNA. Purines are required by all cells for growth and survival and also play a role in signal transduction and translation. Purines and pyrimidines originate primarily from endogenous synthesis, with dietary sources playing only a minor role. The end product of purine metabolism is uric acid (2,6,8-trioxypurine), which must be excreted continuously to avoid toxic accumulation. Disorders of purine and pyrimidine metabolism can involve all organ systems at any age. The diagnosis of the specific disorders of purine and pyrimidine metabolism is based upon the clinical presentation of the patient, determination of specific concentration patterns of purine and pyrimidine metabolites, and confirmatory enzyme assays and/or molecular genetic testing. There are numerous inborn errors of purine and pyrimidine metabolism that have been documented. Clinical features are dependent upon the specific disorder, but represent a broad spectrum of clinical manifestations that may include immunodeficiency, developmental delay, nephropathy, and neurologic involvement. The most commonly described disorder involves a deficiency of hypoxanthine phosphoribosyl transferase (HPRT), the majority of which have classic Lesch-Nyhan syndrome. Lesch-Nyhan syndrome was described in 1964 as the first disorder of purine metabolism. It is an X-linked disorder characterized by severe neurologic impairment, the development of a compulsive self-destructive behavior, and uric acid nephropathy.

Useful For: Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory evaluation of primary and secondary hyperuricemias

Interpretation: Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies at the Mayo Clinic or elsewhere, and a phone number of the laboratory directors in case the referring physician has additional questions.

Reference Values:

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>0-2 years</th>
<th>3-5 years</th>
<th>6-11 years</th>
<th>12-17 years</th>
<th>&gt; or =18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>URIC ACID</td>
<td>&lt; or =2,249 mmol/mol creatinine</td>
<td>&lt; or =1,900 mmol/mol creatinine</td>
<td>&lt; or =1,398 mmol/mol creatinine</td>
<td>&lt; or =698 mmol/mol creatinine</td>
<td>&lt; or =669 mmol/mol creatinine</td>
</tr>
<tr>
<td>HYPOXANTHINE</td>
<td>&lt;53 mmol/mol creatinine</td>
<td>&lt;49 mmol/mol creatinine</td>
<td>&lt;43 mmol/mol creatinine</td>
<td>&lt;36 mmol/mol creatinine</td>
<td>&lt;40 mmol/mol creatinine</td>
</tr>
<tr>
<td>XANTHINE</td>
<td>&lt;49 mmol/mol creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3-5 years: <41 mmol/mol creatinine
6-11 years: <30 mmol/mol creatinine
12-17 years: <16 mmol/mol creatinine
> or =18 years: <51 mmol/mol creatinine

**Clinical References:** Jurecka A: Inborn errors of purine and pyrimidine metabolism. J Inherit Metab Dis 2009;32:247-263

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**FPYRE**

**Pyrethrum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

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**FPYD**

**Pyridostigmine, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis
Synonym(s): Mestinon

30-125 ng/mL plasma in myasthenia gravis patients restores normal neuronal transmission. Specimens must be kept frozen.

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**PLP**

**Pyridoxal 5-Phosphate (PLP), Plasma**

**Clinical Information:** Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5'-phosphate esters. Due to its role as a cofactor in a number of enzymatic reactions, pyridoxal phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid are observed in cases of hypophosphatasia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

**Useful For:** Determining vitamin B6 status, including in persons who present with progressive nerve compression disorders, such as carpal tunnel and tarsal tunnel syndromes Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatasia

**Interpretation:** Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results: If PLP is >100 mcg/L; or -If PLP is >100 mcg/L and PA is < or =30, the increased pyridoxal 5-phosphate is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is >100 mcg/L and PA is 31 to 100 mcg/L; or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L, the increased pyridoxal 5-phosphate is likely related to dietary supplementation; however a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30; or PLP is >100 mcg/L and PA is >100 mcg/L, the
elevated pyridoxal 5-phosphate is likely due to dietary supplementation.

**Reference Values:**
5-50 mcg/L

**Clinical References:**

**B6PA**

**Pyridoxic Acid (PA), Plasma**

**Reference Values:**
Only orderable as part of a profile. For more information see B6PRO / Vitamin B6 Profile (PLP and PA), Plasma.

**P5NT**

**Pyrimidine 5' Nucleotidase, Blood**

**Clinical Information:** Pyrimidine 5' nucleotidase (P5'NT) is involved in the catabolism of RNA which is a normal constituent of reticulocytes but not of mature erythrocytes. A deficiency of P5'NT is evidenced by persistent reticulocytosis.

**Useful For:** Workup of individuals with persistent reticulocytosis

**Interpretation:** Screening test negative for pyrimidine 5'nucleotidase deficiency

**Reference Values:**
Normal


**PDHC**

**Pyruvate Dehydrogenase Complex (PDHC), Fibroblasts**

**Clinical Information:** The pyruvate dehydrogenase complex (PDHC) catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, a critical step in the production of cellular energy. PDHC is a multienzyme complex located in the inner mitochondrial membrane, consisting of 6 different components: pyruvate dehydroxylase (E1, with alpha and beta subunits), dihydrolipoic transacetylase (E2), dihydrolipoyl dehydrogenase (E3), 2 regulatory enzymes (PDH kinase and PDH phosphatase), and E3-binding protein. PDHC deficiency is a mitochondrial disorder with a variable clinical presentation ranging from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. In infants and children with PDHC deficiency, the most common features are delayed development and hypotonia. Seizures and ataxia are also frequent features. Less common manifestations include congenital brain malformations, particularly ventriculomegaly and agenesis of the corpus callosum, or degenerative changes, including Leigh disease. Facial dysmorphism is seen in a small portion of patients. PDHC deficiency is one of the most common causes of primary lactic acidosis in children. The severity of the disease progression is thought to be related to the severity of the lactic acidosis as well as the level of residual enzyme activity. PDHC deficiency can be caused by defects in the E1 alpha, E1 beta, E2, or E3 subunits. The most common cause of PDHC deficiency is a defect in the E1 alpha gene, located on the X chromosome. Both females and males with an E1 alpha gene mutation are affected with PDHC deficiency, thus it is classified as X-linked dominant. Mutations in the E1 alpha gene are typically de novo. The most important initial diagnostic test is the measurement of blood and cerebrospinal fluid lactate and pyruvate, along with a lactate-to-pyruvate (L:P) ratio (typically normal ratio with elevated...
lactate and pyruvate). Additionally, plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma) may detect an increase in alanine. A diagnosis of PDHC deficiency depends on the measurement of enzyme activity in cells or tissues, most commonly in skin fibroblasts.

**Useful For:** Evaluation of patients with a clinical suspicion of a pyruvate dehydrogenase complex deficiency or an energy metabolism disorder

**Interpretation:** When below-normal enzyme activities are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

**Reference Values:**
- >25.00 nmol/min/g protein (Normal)
- 5.00-25.00 nmol/min/g protein (Indeterminate)
- <5.00 nmol/min/g protein (Deficient)

Reference values apply to all ages.

**Clinical References:**

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**Pyruvate Kinase, Erythrocytes**

**Clinical Information:** Deficiencies of most of the enzymes of the Embden-Meyerhof (glycolytic) pathway, including pyruvate kinase (PK), have been reported. PK deficiency, although rare, is the erythrocyte enzyme deficiency most frequently found to be a cause of congenital nonpherocytic hemolytic anemia. It is an autosomal recessive disorder. Thus, the parents of affected patients are heterozygotes. Patients usually present during early childhood with anemia, icterus, and splenomegaly. Hemolytic disease of the newborn is common in persons with PK deficiency.

**Useful For:** Work-up of cases of nonpherocytic hemolytic anemia Investigating families with pyruvate kinase deficiency to determine inheritance pattern and for genetic counseling

**Interpretation:** Most pyruvate kinase (PK) deficient patients have 5% to 25% of normal activity. Elevated PK concentrations can be found in those patients with younger erythrocyte population. This may be due to the patient being a newborn or young red cells are being produced in response to the anemia (reticulocytosis).

**Reference Values:**
- > or =12 months: 6.7-14.3 U/g Hb

Reference values have not been established for patients who are <12 months of age.

Pyruvate, Spinal Fluid

Clinical Information: Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though pyruvate is not diagnostic in itself, analysis with lactate has diagnostic value as many inborn errors of metabolism present with laboratory findings that include lactic acidosis and/or a high lactate:pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and the L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

Useful For: Investigating possible disorders of mitochondrial metabolism, when used in conjunction with cerebrospinal fluid lactate collected at the same time to determine the lactate-to-pyruvate ratio Evaluating patients with neurologic dysfunction and normal blood lactate-to-pyruvate ratios

Interpretation: An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios >20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios <10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found in acutely ill patients.

Reference Values:
0.06-0.19 mmol/L


Pyruvic Acid, Blood

Clinical Information: Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though isolated elevated pyruvate is not diagnostic of any inborn error of metabolism, analysis with lactate may suggest an inborn error of metabolism as some present with lactic acidosis and/or a high lactate-to-pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels, though further confirmatory testing will be required to establish a diagnosis. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild...
ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are
delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations
can include congenital brain malformations, degenerative changes including Leigh disease, and facial
dysmorphism.

Useful For: Screening for possible disorders of mitochondrial metabolism, when used in conjunction
with blood lactate collected at the same time to determine the lactate-to-pyruvate ratio

Interpretation: An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the
respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency.
Respiratory chain defects usually result in L:P ratios >20. A low L:P ratio (disproportionately elevated
pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate
dehydrogenase complex result in L:P ratios <10. The L:P ratio is characteristically normal in other
patients. An artificially high ratio can be found if the patient is acutely ill. Cerebrospinal fluid (CSF) L:P
ratio may assist in evaluation of patients with neurologic dysfunction and normal blood L:P ratios. Blood
and CSF specimens should be collected at the same time.

Reference Values:
0.08-0.16 mmol/L

NIH Unit
0.7-1.4 mg/dL

Clinical References: 1. Munnich A, Rotig A, Cormier-Daire V, Rustin P: Clinical presentation of
respiratory chain deficiency. OMMPID Accessed 10 Nov 2015. Available from URL:
acidemia: disorders of pyruvate carboxylase and pyruvate dehydrogenase. OMMPID. Accessed 10 Nov
2015. Available from URL:
Oxidative Phosphorylation Diseases. OMMPID Accessed 10 Nov 2015. Available from URL:

Q Fever Antibody, IgG and IgM, Serum

Clinical Information: Q fever, a rickettsial infection caused by Coxiella burnetii, has been
recognized as a widely distributed zoonosis with the potential for causing both sporadic and epidemic
disease. The resistance of Coxiella burnetii to heat, chemical agents, and desiccation allows the agent to
survive for extended periods outside the host. The infection is spread by the inhalation of infected
material, mainly from sheep and goats. They shed the organism in feces, milk, nasal discharge, placental
tissue, and amniotic fluid. The clinical spectrum of disease ranges from unapparent to fatal. Respiratory
manifestations usually predominate; endocarditis and hepatitis can be complications. During the course of
the infection, the outer membrane of the organism undergoes changes in its lipopolysaccharide structure,
called phase variation. Differences in phase I and phase II antigen presentation can help determine if the
infection is acute or chronic: -In acute Q fever, the phase II antibody is usually higher than the phase I
titer, often by 4-fold, even in early specimens. Although a rise in phase I as well as phase II titers may
occur in later specimens, the phase II titer remains higher. -In chronic Q fever, the reverse situation is
generally seen. Serum specimens drawn late in the illness from chronic Q fever patients demonstrate
significantly higher phase I titers, sometimes much greater than 4-fold. -In the case of chronic
granulomatous hepatitis, IgG and IgM titers to phase I and phase II antigens are quite elevated, with phase
II titers generally equal to or greater than phase I titers. -Titers seen in Q fever endocarditis are similar in
magnitude, although the phase I titers are quite often higher than the phase II titers.

Useful For: Diagnosing Q fever

Interpretation: Phase I antibody titers greater than or equal to phase II antibody titers are consistent
with chronic infection or convalescent phase Q fever. Phase II antibody titers greater than or equal to
phase I antibody titers are consistent with acute/active infection. A negative result argues against Coxiella
burnetii infection. If early acute Q fever infection is suspected, draw a second specimen 2 to 3 weeks later
and retest. In Q fever sera, it is common to see IgG titers of 1:128 or greater to both phase I and phase II antibody titers. IgG class antibody titers appear very early in the disease, reaching maximum phase II titers by week 8 and persisting at elevated titers for longer than a year. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence. In Q fever sera, it is common to see IgM titers of > or =1:64. IgM class antibody titers appear very early in the disease, reaching maximum phase II titers by week 3 and declining to very low levels by week 14. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence.

**Reference Values:**

- **Q FEVER PHASE I ANTIBODY, IgG**
  - <1:16

- **Q FEVER PHASE II ANTIBody, IgG**
  - <1:16

- **Q FEVER PHASE I ANTIBODY, IgM**
  - <1:16

- **Q FEVER PHASE II ANTIBODY, IgM**
  - <1:16

**Clinical References:**


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**Quad Screen (Second Trimester) Maternal, Serum**

**Clinical Information:** Multiple marker serum screening has become a standard tool used in obstetrical care to identify pregnancies that may have an increased risk for certain birth defects, including neural tube defects (NTDs), Down syndrome, and trisomy 18. The screen is performed by measuring analytes in maternal serum that are produced by the fetus and the placenta. The analyte values along with maternal demographic information such as age, weight, gestational age, diabetic status, and race are used together in a mathematical model to derive a risk estimate. The laboratory establishes a specific cutoff for each condition, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered. Analytes:

- **Alpha-Fetoprotein (AFP):** AFP is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from a nonpregnancy level of 0.2 to about 250 ng/mL at 32 weeks gestation. If the fetus has an open NTD, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal distress situations such as threatened abortion, and fetal demise also may show AFP elevations. Increased maternal serum AFP values also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP values have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18. Estriol (uE3): Estriol, the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the intact feto-placental unit. Estriol exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of unconjugated estriol in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates estriol to make it more water soluble for urinary excretion. Estriol levels increase during the course of pregnancy. Decreased unconjugated estriol has been shown to be a marker for Down syndrome and trisomy 18. Low levels of estriol also have been associated with
overestimation of gestation, pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Human Chorionic Gonadotropin (Total Beta-hCG: ThCG) hCG is a glycoprotein consisting of 2 noncovalently bound subunits. The alpha subunit is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. The CGA gene (glycoprotein hormones, alpha polypeptide) is thought to have developed through gene duplication from the LH gene in a limited number of mammalian species. hCG only plays an important physiological role in primates (including humans), where it is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum, and hence, progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with Down syndrome, while decreased levels may be seen in trisomy 18. Elevations of hCG also can be seen in multiple pregnancies, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetalis. Inhibin A Inhibins are a family of heterodimeric glycoproteins, primarily secreted by ovarian granulosa cells and testicular Sertoli cells, which consist of disulfide-linked alpha and beta subunits. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta A or a beta B chain, they are designated as inhibin A or inhibin B, respectively. Together with the related activins, which are homodimers or heterodimers of beta A and B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the feto-placental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibin A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibin A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibin A levels are typically higher in Down syndrome pregnancies). However, despite their similar behavior, measuring maternal serum inhibin A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for Down syndrome.

Useful For: Prenatal screening for open neural tube defect (alpha-fetoprotein only), Down syndrome (alpha-fetoprotein, human chorionic gonadotropin, estriol, and inhibin A) and trisomy 18 (alpha-fetoprotein, human chorionic gonadotropin, and estriol)

Interpretation: Neural Tube Defects (NTD): A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of NTD. A screen-positive result indicates that the calculated AFP MoM is > or =2.50 MoM, and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual's pretest risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of NTD, but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with NTD have elevated AFP, MoM values >2.5. Down Syndrome and Trisomy 18: A screen-negative result indicates that the calculated screen risk is below the established cutoff of 1/270 for Down syndrome and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 18 or Down syndrome. When a Down syndrome second trimester risk cutoff of 1/270 is used for follow-up, the combination of maternal age, AFP, estriol, hCG, and inhibin A has an overall detection rate of approximately 77% to 81% with a false-positive rate of 6% to 7%. In practice, both the detection rate and false-positive rate increase with age. The detection rate ranges from 66% (early teens) to 99% (late 40s), with false-positive rates of between 3% and 62%, respectively. The detection rate for trisomy 18 is 60% to 80% using a second trimester cutoff of 1/100. Follow-up: Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (maternal date of birth, gestational dating, etc.). If any information is incorrect, the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD or trisomy 21 screen-positive results. Many pregnancies affected with trisomy 18 are small for gestational age. Recalculations that lower the gestational age may decrease the detection rate.
for trisomy 18. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTD) are typically offered.

Reference Values:

**NEURAL TUBE DEFECTS**

An AFP multiple of the median (MoM) <2.5 is reported as screen negative. AFP MoMs ≥2.5 (singleton and twin pregnancies) are reported as screen positive.

**DOWN SYNDROME**

Calculated screen risks <1/270 are reported as screen negative, risks ≥1/270 are reported as screen positive.

**TRISOMY 18**

Calculated screen risks <1/100 are reported as screen negative, risks ≥1/100 are reported as screen positive.

An interpretive report will be provided.

**Clinical References:**


**QuantiFERON-TB Gold In-Tube for Detection of Latent Tuberculosis, Blood**

**Clinical Information:** Latent tuberculosis infection (LTBI) is a noncommunicable, asymptomatic condition that persists for many years in individuals and may progress to tuberculosis (TB) disease. The main purpose of diagnosing LTBI is to consider medical treatment for preventing active tuberculosis disease. Until recently, the tuberculin skin test (TST) was the only method available for diagnosing LTBI. Unfortunately, the TST is a subjective test that can be falsely positive for individuals who have been vaccinated with bacille Calmette-Guerin (BCG), are infected with other mycobacteria than Mycobacterium tuberculosis complex, or due to other factors such as a digital palpitation error when reading the test. The QuantiFERON-TB Gold In-Tube test is a measure of cell-mediated immune response to antigens simulating the mycobacterial proteins ESAT-6, CFP-10, and TB7.7. Individuals infected with Mycobacterium tuberculosis complex organisms including Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti, and Mycobacterium canetti usually have lymphocytes in their blood that recognize these specific antigens. The recognition process involves the generation and secretion of the cytokine, interferon-gamma (IFN-gamma). The detection and quantification of IFN-gamma by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to TB antigens that are associated with Mycobacterium tuberculosis complex infection. The ESAT-6, CFP-10, and TB7.7 antigens are absent from the Mycobacterium bovis BCG strains and from most nontuberculous mycobacteria with the exception of Mycobacterium kansasi, Mycobacterium szulgai, and Mycobacterium marinum. Numerous studies have demonstrated that ESAT-6, CFP-10, and TB7.7 stimulate IFN-gamma responses in T cells from individuals infected with Mycobacterium tuberculosis but usually not from uninfected or BCG-vaccinated persons without disease or risk for LTBI.
**Useful For:** Indirect test for Mycobacterium tuberculosis complex infection (latent tuberculosis infection)

**Interpretation:** This is a qualitative test. The TB Antigen (Ag)-nil IU/mL value should not be used to differentiate active from latent disease or to monitor disease progression or response to therapy. Diagnosis or exclusion of tuberculosis (TB) and assessing the probability of latent tuberculosis infection (LTBI), require a combination of epidemiologic, historical, clinical, radiologic, and additional laboratory findings (eg, mycobacterial smear and/or culture) be taken into account when interpreting QuantiFERON-TB Gold results. The nil value is used to determine the background, circulating interferon-gamma level in the patient. For the QuantiFERON-TB Gold test to be valid, the nil value must be < or =8.0 IU/mL. The mitogen minus nil value is used to assure that the patient able to produce an interferon-gamma response to a universal stimulant (phytohemagglutinin). For the QuantiFERON-TB Gold test to be valid, the mitogen value must be at least 0.5 IU/mL higher than the nil value. The QuantiFERON-TB Gold test is considered positive if the interferon-gamma response in the TB antigen minus nil value is at least 0.35 IU/mL.

**Reference Values:**

**Negative**

**Clinical References:**

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**Queen Palm, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
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<tr>
<td>0</td>
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<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


FQUET

Quetiapine (Seroquel)

Reference Values:
Units:  ng/mL

Therapeutic and toxic ranges have not been established. Expected steady-state Quetiapine plasma levels in patients receiving recommended daily dosages: 100 - 1000 ng/mL.

QUIND

Quinidine, Serum

Clinical Information: Quinidine is indicated for atrial fibrillation and flutter, and life-threatening ventricular arrhythmia. Optimal serum concentrations are in the range of 2.0 to 5.0 mcg/mL, with toxicity apparent at levels > or =6.0 mcg/mL. Symptoms of toxicity (cinchonism) include tinnitus, light-headedness, premature ventricular contractions, and atrioventricular block. Gastrointestinal distress is a frequent side effect, which becomes more severe and is associated with nausea and vomiting at higher drug concentrations. The half-life of quinidine is 6 to 8 hours, and the drug lacks any significant active metabolites. Physiologic processes that generally reduce hepatic metabolism and renal clearance increase serum quinidine levels, while comedication with cytochrome p450 (CYP) enzyme inducers enhances clearance and results in lower blood concentrations.

Useful For: Assessing and adjusting dosage for optimal therapeutic level Assessing toxicity

Interpretation: Optimal response to quinidine occurs when the serum level is between 2.0 to 5.0 mcg/mL.

Reference Values:
Therapeutic: 2.0-5.0 mcg/mL
Critical value: > or =6.0 mcg/mL


FQUIN

Quinoa (Chenopodium quinoa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L
Rabbit Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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| 6     | > or =100| Strongly positive Reference values apply to all ages.


Rabbit Meat, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Rabbit Serum Proteins, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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</table>

Reference values apply to all ages.
Rabbit Urine Proteins, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

**Class IgE kU/L**  
0  Negative  
1  0.35-0.69  Equivocal  
2  0.70-3.49  Positive  
3  3.50-17.4  Positive  
4  17.5-49.9  Strongly positive  
5  50.0-99.9  Strongly positive  
6  > or =100  Strongly positive Reference values apply to all ages.

### Rabies Antibody Endpoint

**Interpretation**: Quantitative results. For those who want to know their exact titer between the reportable range. RFFIT stands for Rapid Fluorescent Foci Inhibition Test. It is a serum neutralization (inhibition) test, which means it measures the ability of rabies specific antibodies to neutralize rabies virus and prevent the virus from infecting cells. The antibodies are called rabies virus neutralizing antibodies (RVNA).

**Reference Values**:
- Reportable range is 0.1 to 15.0 IU/mL
- Less than 0.1 IU/mL: Below detection limit

In humans a results of 0.5 IU/mL or higher is considered an acceptable response to rabies vaccination according to the World Health Organization (WHO) guidelines; see WHO and Advisory Committee on Immunization Practices documents for additional guidance.

### Radish (Raphanus sativus) IgE

**Interpretation**: Class IgE (kU/L) Comment
- 0 <0.35 Below Detection
- 1 0.35 – 0.69 Low Positive
- 2 0.70 – 3.49 Moderate Positive
- 3 3.50 – 17.49 Positive
- 4 17.50 – 49.99 Strong Positive
- 5 50.00 – 99.99 Very Strong Positive
- 6 >99.99 Very Strong Positive

**Reference Values**:
- <0.35 kU/L

### RAF1 Gene, Known Mutation, Blood

**Clinical Information**: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be underestimated. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous, Costello, Williams, Aarskog, and multiple lentigines (LEOPARD: lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-MAPK pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 approximately 10%, and KRAS less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in 30% to 75% of families. The RAF1 gene comprises 17 exons and encodes the Raf-1 protein, which is 648 amino acids and has 3 domains: CR1, CR2, and CR3. Reported mutations in RAF1 are missense mutations, and cluster within the CR2 and CR3 domains. NS-associated RAF1 mutations are predicted to cause a gain-of-function of the protein. Some studies have
shown that there is a genotype-phenotype correlation associated with NS. RAF1 mutations appear to be correlated with hypertrophic cardiomyopathy (HCM). In a study by Pandit et al.(1) 18 of 19 (95%) subjects with NS or LEOPARD syndrome with a RAF1 mutation showed HCM, compared with the 18% prevalence of HCM among individuals with NS in general. In contrast, PTPN11 mutations are rarely associated with HCM, but are frequently associated with pulmonary stenosis. Mutations in RAF1 have also been associated with LEOPARD syndrome, an autosomal dominant disorder sharing several clinical features with NS characterized by lentigines and cafe-au-lait spots, facial anomalies, and cardiac defects. Additionally, a RAF1 mutation was identified in 1 case of nonsyndromic HCM.(1) Genetic testing for RAF1 mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Genetic testing of individuals at risk for a known RAF1 mutation that has been identified in a family member

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**RAF1, Full Gene Sequence, Blood**

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be underestimated. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-MAPK pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals with NS. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 approximately 10%, and KRAS less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in 30% to 75% of families. The RAF1 gene comprises 17 exons and encodes the Raf-1 protein, which is 648 amino acids and has 3 domains: CR1, CR2, and CR3. Reported mutations in RAF1 are missense mutations, and cluster within the CR2 and CR3 domains. NS-associated RAF1 mutations are predicted to cause a gain-of-function of the protein. Some studies have shown that there is a genotype-phenotype correlation associated with NS. RAF1 mutations appear to be correlated with hypertrophic cardiomyopathy (HCM). In a study by Pandit et al(1), 18 of 19
subjects with NS or LEOPARD syndrome with a RAF1 mutation showed HCM, compared with the 18% prevalence of HCM among individuals with NS in general. In contrast, PTPN11 mutations are rarely associated with HCM, but are frequently associated with pulmonary stenosis. Mutations in RAF1 have also been associated with LEOPARD syndrome, an autosomal dominant disorder sharing several clinical features with NS characterized by lentigines and cafe-au-lait spots, facial anomalies, and cardiac defects. Additionally, a RAF1 mutation was identified in 1 case of nonsyndromic hypertrophic cardiomyopathy. (1) Genetic testing for RAF1 mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

Useful For: Aiding in the diagnosis of RAF1-associated Noonan syndrome and LEOPARD syndrome

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics recommendations. (2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


FRAJI 57860

Raji Cell Immune Complex Assay

Reference Values: 
<= 37 ugE/mL

Many autoimmune disorders, chronic infections and malignancies are associated with circulating immune complexes. Quantitation of immune complexes assists in staging immunologic disorders.

RASE 82366

Rape Seed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


RWEED
82616

Rape Weed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
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1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


MAL 9240
Rapid Malaria/Babesia Smear
Clinical Information: Malaria is a major tropical disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. Ninety percent of the deaths occur in sub-Saharan Africa and most of these occur in children <5 years old; it is the leading cause of mortality in this age group. This disease is also widespread in Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers to, and visitors from endemic areas. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a similar parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating Plasmodium falciparum and Plasmodium knowlesi from other species is important since both can cause life-threatening infections. In addition, Plasmodium falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Babesiosis is an emergent zoonosis caused by an intraerythrocytic protozoan in the genus Babesia. Babesia microti is responsible for the vast majority of human cases in the United States, with "hot spots" of disease along the Northeast Coast (e.g., Martha's Vineyard, Long Island, and Nantucket) and Midwest states, although the distribution of disease is spreading. In addition, a small number of cases of Babesia duncani and Babesia duncani-like human infection (WA and CA strains) have been reported along Pacific Coast states from Washington to northern California, and Babesia divergens/Babesia divergens-like strains have been isolated from humans in Missouri (MO-1 strain), Kentucky, and Washington. At this time, only Babesia microti is a nationally notifiable disease. Babesia microti shares a tick vector with Borrelia burgdorferi and Anaplasma phagocytophilum, the causative agents of Lyme disease and human granulocytic anaplasmosis (HGA), respectively. Recent studies suggest that exposure to Babesia microti is quite common in areas endemic for Lyme disease and anaplasmosis, so it is prudent to consider testing for all 3 diseases concurrently. Less commonly, babesiosis may be acquired through blood transfusion, and therefore donor units are tested for this parasite in some endemic areas. Most patients with babesiosis have a mild illness or are asymptomatic, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of Plasmodium and Babesia species. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. This test can also detect trypanosomes that cause Chagas disease (Trypanosoma cruzi) and African sleeping sickness (Trypanosoma brucei), as well as some species of filariae. If filarial infection is suspected, FIL / Filaria, Blood is recommended since it is more sensitive than the traditional blood smear examination. Examination of the thin film allows for calculation of malaria percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis. The percentage parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Malarial gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalarial drugs.

Useful For: The rapid and accurate detection and species identification of Plasmodium Detection of Babesia, trypanosomes, and some species of microfilariae

Interpretation: A positive smear indicates infection with the identified species of Plasmodium or with Babesia. Species identification can indicate the appropriate antimalarial therapy.
Reference Values:
Negative
If positive, organism identified and percent parasitemia calculated, if applicable.


Rapid Plasma Reagin (RPR), Response to Therapy, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that Treponema pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Patients with primary or secondary syphilis should be reexamined clinically and serologically 6 months and 12 months following treatment. Typically, rapid plasma reagin titers decrease following successful treatment but this may occur over a period of months to years.

Useful For: Determining the current disease status and evaluating response to therapy for syphilis

Interpretation: Treatment response is generally indicated by a 4-fold (2-tube dilution) reduction in rapid plasma reagin (RPR) titer (eg, 1:32 to 1:8). For proper interpretation of RPR results, titers should be obtained using the same testing method and, preferably, at the same testing laboratory. Failure of nontreponemal test titers to decline 4-fold within 6 months after therapy for primary or secondary syphilis might be indicative of treatment failure. Persons for whom titers remain serofast should be reevaluated for HIV infection.

Reference Values:
Negative


RAS/RAF Targeted Gene Panel by Next Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with solid tumors. These data can also be used to help determine clinical trial eligibility for patients with mutations in genes not amenable to current FDA-approved targeted therapies. EGFR is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with colorectal cancer. Assessment for BRAF mutations has clinical utility in that it is a predictor of response to antmutant BRAF therapy. BRAF is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success.
with increases both in progression-free and overall survival in patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components. See Targeted Gene Regions Interrogated by RAS/RAF Gene Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously; identifying mutations that may help determine prognosis for patients with solid tumors; identifying specific mutations within genes known to be associated with response or resistance to specific cancer therapies.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**FRASP**

**Raspberry IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**RASP**

**Raspberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**RAT 82725**

**Rat Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**RTSP 82793**

**Rat Serum Protein, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effectors (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.

**Rat Urine Protein, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms; Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
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<td>Positive</td>
</tr>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


**Recombx MaTa Autoantibody Test**

**Reference Values:**

A final report will be attached in MayoAccess.
Red Blood Cell (RBC) Enzyme Evaluation

Clinical Information: All enzyme defects, including erythrocyte enzyme errors, are inherited; some are sex-linked and located on the X chromosome. Some family members have no hematologic abnormalities, while others have a hemolytic anemia. For a number of RBC enzyme defects (eg, deficiencies of hexokinase, glucose phosphate isomerase, pyruvate kinase), the sole clinical manifestation is hemolytic anemia. Glucose-6-phosphate dehydrogenase deficiency is the most common metabolic error of the red cell and presents with acute hemolytic anemia in response to oxidant stress (eg, drugs, acute infections, fava bean ingestion). This is a consultative evaluation looking at red cell enzyme defects as the cause for early red cell destruction.

Useful For: Identifying defects of red cell enzyme metabolism Evaluating patients with hemolytic anemia

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values: Definitive results and an interpretive report will be provided.


Red Blood Cell Membrane Evaluation, Blood

Clinical Information: The hemolytic anemias are a group of anemias that are characterized by an increased destruction of RBCs. Anemias may be divided into inherited or acquired. Hereditary spherocytosis (HS) is inherited as a non-sex-linked dominant trait. HS is caused by a RBC membrane defect. The RBCs are spherocytic in shape and show an increased rate of destruction. HS can result from abnormalities involving several red cell membrane proteins, such as band 3, spectrin, and ankyrin. Most often HS is diagnosed in childhood, adolescence, or early adult life. The diagnosis of HS is usually made by a combination of patient and family history, laboratory evidence of hemolysis, and review of a peripheral blood smear. The osmotic fragility test is usually markedly abnormal in these cases. However, factors such as age, sex, and medications can affect the osmotic fragility test. This evaluation combines osmotic fragility testing with a flow cytometry assay to provide complementary information in the evaluation of patients with suspected HS.

Useful For: Investigation of suspected red cell membrane disorder such as hereditary spherocytosis or hereditary pyropoikilocytosis

Interpretation: An interpretive report will be provided.

Reference Values:

> or =12 months:

0.50 g/dL NaCl (unincubated): 3-53 % hemolysis
0.60 g/dL NaCl (incubated): 14-74 % hemolysis
0.65 g/dL NaCl (incubated): 4-40 % hemolysis
0.75 g/dL NaCl (incubated): 1-11 % hemolysis

An interpretive report will be provided.

Reference values have not been established for patients who are <12 months of age.

## Red Currant, IgE

### Clinical Information:
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

### Useful For:
Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

### Interpretation:
Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.10</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal/Borderline</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:

## Red Snapper (Lutjanus spp) IgE

### Interpretation:
Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

### Reference Values:

<0.35 kU/L

## Red Sorrel, IgE

### Clinical Information:
Clinical manifestations of immediate hypersensitivity (allergic) diseases are...
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Red Top, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to...
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</tr>
</tbody>
</table>

Reference values apply to all ages.


**Reducing Substance, Feces**

**Clinical Information:** Sugars (e.g., glucose, galactose, fructose, maltose, lactose, and pentose) are characterized as reducing substances based on their ability to reduce cupric ions to cuprous ions. Fecal reducing substances may be increased in carbohydrate malabsorption syndromes.

**Useful For:** Diagnosing intestinal malabsorption in children Assisting in the differentiation between osmotic and nonosmotic diarrhea Screening test for: -Diarrhea from disaccharidase deficiencies, (eg, lactase deficiency) -Monosaccharide malabsorption

**Interpretation:** Negative: negative Normal: <0.25 g/dL (trace) Suspicious: 0.25 to 0.50 g/dL (grade 1) Abnormal: >0.50 g/dL (grade 2-4)

**Reference Values:**

Negative or trace


**Relative B-Cell Subset Analysis Percentage**

**Clinical Information:** The adaptive immune response includes both cell-mediated (mediated by T cells and NK cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are of 3 subsets: marginal zone B cells (MZ or nonswitched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both, result in immune deficiency states and...
increased susceptibility to infections. These decreases may be either primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1:25,000 to 1:50,000.(1) CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years of age, or occasionally even later. Four different genetic defects have been associated with CVID, including mutations in the ICOS, CD19, BAFF-R, and TACI genes. The first 3 genetic defects account for approximately 1% to 2%, and TACI mutations account for 8% to 15% of CVID cases. CVID is characterized by hypogammaglobulinemia usually involving most or all of the Ig classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1,2) B-cell numbers may be normal or decreased. A minority of CVID patients (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency.(1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4:CD8 ratio (<1). Studies have shown the clinical relevance of classifying CVID patients by assessing B-cell subsets, since changes in different B-cell subsets are associated with particular clinical phenotypes or presentations.(3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA.(5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects at mutations in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes.(5) Mutations in CD40L and NEMO are inherited in an X-linked fashion, while mutations in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increase in nonswitched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depleting therapies, such as Rituxan (Rituximab) and Zevalin (Ibritumomab tiuxetan).

**Useful For:** Screening for humoral or combined immunodeficiencies, including common variable immunodeficiency (CVID), hyper IgM syndrome, among others, where B-cell subset distribution information is desired Assessing B-cell subset reconstitution after hematopoietic cell (HCT) or bone marrow transplant Assessing B-cell subset reconstitution following recovery of B cells after B-cell-depleting immunotherapy

**Interpretation:** The assay provides semiquantitative (%) information on the various B-cell subsets. Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: -CD19+=B cells expressing CD19 as a percent of total lymphocytes -CD19+ CD27+=total memory B cells -CD19+ CD27+ IgD+ IgM+=marginal zone or non-switched memory B cells -CD19+ CD27+ IgD- IgM+=memory B cells -CD19+ CD27+ IgD- IgM+ IgM-only B cells -CD19+ CD27+ IgD- IgM+=class-switched memory B cells -CD19+ IgM+=IgM B cells -CD19+ CD38+ IgM+=transitional B cells -CD19+ CD38+ IgM+=plasmablasts -CD19+ CD21-=CD21-negative B cells -CD19+ CD21+=CD21-positive B cells -CD19+ CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes For isotype class-switching and memory B-cell analyses, the data will be reported as being consistent or not consistent with a quantitative defect in memory subsets and/or class switching. If a defect is present in any of these B-cell subpopulations, further correlation with clinical presentation and additional functional, immunological, and genetic laboratory studies will be suggested, if appropriate.

**Reference Values:** The appropriate age-related reference values will be provided on the report.


**Renal Pathology Consultation, Wet Tissue**

**Clinical Information:** The Mayo Renal Pathology service is staffed by board-certified pathologists who have a special interest in non-neoplastic diseases of the kidney. Kidney biopsy has proven to be of value in the clinical evaluation and management of patients with kidney disease, including acute and chronic renal insufficiency, nephrotic syndrome, nephritic syndrome, proteinuria and hematuria, and in the overall management of renal transplant recipients. Optimal interpretation of a kidney biopsy requires integration of clinical and laboratory results with light microscopic, immunofluorescent histology, and electron microscopy findings.

**Useful For:** The evaluation and management of patients with kidney disease Following the progression of known renal disease and/or response to therapy Determining the cause of dysfunction in the transplanted kidney (allograft)

**Interpretation:** A verbal report of the findings is typically communicated by phone to the submitting nephrologist, and an initial report based on the light microscopic and immunofluorescent histology interpretation is also faxed to the nephrologist. A report is also sent to the submitting pathology laboratory. Representative electron microscopy images and significant positive immunofluorescent stain findings can be provided on a CD upon request. In most cases, the electron microscopy results are reported as an addendum and a final report is issued including these findings. This final report is again faxed to the submitting nephrologist and mailed to the submitting pathology laboratory, along with a representative set of the light microscopy slides.

**Reference Values:**
An interpretive report will be provided.


**Renin Activity, Plasma**

**Clinical Information:** The renal juxtaglomerular apparatus generates renin, an enzyme that converts angiotensinogen to angiotensin I. The inactive angiotensin I is enzymatically converted to the active octapeptide angiotensin II, a potent vasopressor responsible for hypertension of renal origin. Angiotensin II also stimulates the zona glomerulosa of the adrenal cortex to release aldosterone. Renin secretion by the kidney is stimulated by a fall in glomerular blood pressure, by decreased sodium concentration at the macula densa at the distal tubule, or by stimulation of sympathetic outflow to the kidney, such as in renal vascular diseases.

**Useful For:** Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:** A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. A SA/PRA ratio > or =20 and SA > or =15 ng/dL indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies in Special Instructions.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1689
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Renin Activity (mean)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>4.6 ng/mL/hour</td>
<td>1.4-7.8 ng/mL/hour</td>
</tr>
<tr>
<td>3-5 years</td>
<td>2.5 ng/mL/hour</td>
<td>1.5-3.5 ng/mL/hour</td>
</tr>
<tr>
<td>6-8 years</td>
<td>1.4 ng/mL/hour</td>
<td>0.8-2.0 ng/mL/hour</td>
</tr>
<tr>
<td>9-11 years</td>
<td>1.9 ng/mL/hour</td>
<td>0.9-2.9 ng/mL/hour</td>
</tr>
<tr>
<td>12-17 years</td>
<td>1.8 ng/mL/hour</td>
<td>1.2-2.4 ng/mL/hour</td>
</tr>
</tbody>
</table>

Mean data not standardized as to time of day or diet. Infants were supine, children sitting.

Na-depleted, upright (peripheral vein specimen)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Renin Activity (mean)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 years</td>
<td>10.8 ng/mL/hour</td>
<td>2.9-24.0 ng/mL/hour</td>
</tr>
<tr>
<td>&gt; or =40 years</td>
<td>5.9 ng/mL/hour</td>
<td>&lt; or =0.6-4.3 ng/mL/hour</td>
</tr>
<tr>
<td>18-39 years</td>
<td>1.9 ng/mL/hour</td>
<td>&lt; or =0.6-3.0 ng/mL/hour</td>
</tr>
</tbody>
</table>


### Reptilase Time, Plasma

**Clinical Information:** Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of any of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time (PT) and activated partial thromboplastin time (APTT) are first-order tests for coagulation abnormalities and are prolonged in many bleeding disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. The thrombin time (TT) test is used to identify the cause of prolonged APTT or dilute Russell's viper venom time (DRVVT). Reptilase time (RT) test is used to evaluate a prolonged TT. Reptilase is a thrombin-like enzyme isolated from the venom of Bothrops atrox. Thrombin splits small fibrinopeptides A and B from fibrinogen molecules, producing fibrin monomer, which polymerizes to form a clot. Reptilase, however, splits off fibrinopeptide A but not B, which results in fibrin polymerization. In contrast to thrombin and the TT test which are inhibited by heparin, the RT is normal in the presence of heparin. Similar to the TT test, the RT is prolonged in the presence of hypofibrinogenemia and dysfibrinogenemia.

**Useful For:** Evaluation of a prolonged thrombin time (TT): It is mainly used to confirm or exclude the presence of heparin in the specimen or specimen type Evaluating hypofibrinogenemia or dysfibrinogenemia in conjunction with the TT and fibrinogen assay

**Interpretation:** As seen in the following table, reptilase time can help distinguish among the various causes of a prolonged thrombin time (TT). Thrombin Time Reptilase Time Causes Remarks Prolonged Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrinogen split products (FSP) Ascertain by FSP or D-dimer assay

**Reference Values:**

14-23 seconds

**Clinical References:** 1. Greaves M, Preston FE: Approach to the bleeding patient. In Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Fourth edition. Edited by RW Colman, J Hirsh,
Respiratory Profile, Region 1, North Atlantic (CT, MA, ME, NJ, NH, NY, PA, RI, VT)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the North Atlantic region including Connecticut, Maryland, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
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<td>6</td>
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Reference values apply to all ages. Total IgE:
Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months</td>
<td>&lt; or =13</td>
</tr>
<tr>
<td>6-11 months</td>
<td>&lt; or =34</td>
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<tr>
<td>1 and 2 years</td>
<td>&lt; or =97</td>
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<tr>
<td>3 years</td>
<td>&lt; or =199</td>
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<tr>
<td>4-6 years</td>
<td>&lt; or =307</td>
</tr>
<tr>
<td>7 and 8 years</td>
<td>&lt; or =403</td>
</tr>
<tr>
<td>9-12 years</td>
<td>&lt; or =696</td>
</tr>
<tr>
<td>13-15 years</td>
<td>&lt; or =629</td>
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<tr>
<td>16 and 17 years</td>
<td>&lt; or =537</td>
</tr>
<tr>
<td>18 years and older</td>
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</tr>
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RPR10 62056

Respiratory Profile, Region 10, Southwestern Grasslands (OK, TX)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Southwestern Grasslands region including Oklahoma and Texas

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases,
including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

Class IgE kU/L  Interpretation
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1  0.35-0.69  Equivocal
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3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages. Total IgE:

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</tbody>
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**Respiratory Profile, Region 11, Rocky Mountain (AZ [Mt]; CO; ID [Mt]; NM, UT [Mt]; WY)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Rocky Mountain region including Arizona, Colorado, Idaho, New Mexico, Utah and Wyoming

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
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Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
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**Clinical References:** 1. Homburger HA: Allergic diseases. In Clinical Diagnosis and Management
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Useful For: Assessing sensitization to various inhalant allergens commonly found in the Arid Southwest region including the southern Arizona desert and the southern California desert

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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**Respiratory Profile, Region 13, Southern Coastal California**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Southern Coastal California region

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may
be responsible for eliciting signs and symptoms.

Reference Values:
Class IgE kU/L  Interpretation
0       Negative
1 0.35-0.69  Equivocal
2 0.70-3.49  Positive
3 3.50-17.4  Positive
4 17.5-49.9  Strongly positive
5 50.0-99.9  Strongly positive
6 > or =100  Strongly positive Reference values apply to all ages. Total IgE:

Results Reported in kU/L
Age     Reference interval
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3 years < or =199
4-6 years < or =307
7 and 8 years  < or =403
9-12 years < or =696
13-15 years < or =629
16 and 17 years  < or =537
18 years and older  < or =214


Respiratory Profile, Region 14, Central California
Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases,
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in Central California

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages. Total IgE:

Results Reported in kU/L

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**Respiratory Profile, Region 15, Intermountain West (Southern ID, NV)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Intermountain West region including southern Idaho and Nevada

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages.

Total IgE: Results Reported in kU/L

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Current as of July 8, 2016 11:28 am CDT

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Inland Northwest region including Oregon and central and east Washington.

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Pacific Northwest including the region of Northwestern California, Western Oregon and Washington

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<td>9-12 years</td>
<td>&lt; or =696</td>
</tr>
<tr>
<td>13-15 years</td>
<td>&lt; or =629</td>
</tr>
<tr>
<td>16 and 17 years</td>
<td>&lt; or =537</td>
</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Alaska

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

<table>
<thead>
<tr>
<th>Class/Interpretation</th>
<th>IgE kU/L</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td>&lt; or =13</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
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</tr>
<tr>
<td>7 and 8 years</td>
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</table>

Respiratory Profile, Region 19, Puerto Rico

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Puerto Rico

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Mid-Atlantic
region including the District of Columbia, Delaware, Maryland, North Carolina and Virginia

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
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</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>


**Respiratory Profile, Region 3, South Atlantic (GA, N.FA, SC)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the South Atlantic region including Georgia, Northern Florida and South Carolina

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive Reference values apply to all ages. Total IgE:</td>
</tr>
</tbody>
</table>

Results Reported in kU/L

<table>
<thead>
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<tr>
<td>4-6 years</td>
<td>&lt; or =307</td>
</tr>
<tr>
<td>7 and 8 years</td>
<td>&lt; or =403</td>
</tr>
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<td>9-12 years</td>
<td>&lt; or =696</td>
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</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>

**Respiratory Profile, Region 4, Sub-tropic Florida (Florida S. of Orlando)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in sub-tropic Florida, which is south of Orlando

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages. Total IgE:</td>
</tr>
</tbody>
</table>

Results Reported in kU/L
Age | Reference interval
---|-------------------
0-5 months | < or =13
6-11 months | < or =34
1 and 2 years | < or =97
3 years | < or =199
4-6 years | < or =307
7 and 8 years | < or =403
9-12 years | < or =696
13-15 years | < or =629
16 and 17 years | < or =537
18 years and older | < or =214


**Respiratory Profile, Region 5, Ohio Valley (IN, KY, OH, TN, WV)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Ohio Valley region including Indiana, Kentucky, Ohio, Tennessee and West Virginia

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may
be responsible for eliciting signs and symptoms.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages. Total IgE:

Results Reported in kU/L

Age Reference interval
0-5 months < or =13
6-11 months < or =34
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3 years < or =199
4-6 years < or =307
7 and 8 years < or =403
9-12 years < or =696
13-15 years < or =629
16 and 17 years < or =537
18 years and older < or =214


Respiratory Profile, Region 6, South Central (AL, AR, LA, MS)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases,
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mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually
manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the South Central
region including Alabama, Arkansas, Louisiana and Mississippi

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases,
including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and
malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an
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Results Reported in kU/L

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<td>18 years and older</td>
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**Clinical References:** 1. Homburger HA: Allergic diseases. In Clinical Diagnosis and Management
Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148
Clinic Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Northern Midwest region including Michigan, Minnesota, and Wisconsin.

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tr>
<td>0</td>
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**Respiratory Profile, Region 8, Central Midwest (IA, IL, MO)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeiciencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Central Midwest region including Iowa, Illinois and Missouri

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeiciencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Respiratory Profile, Region 9, Great Plains (KS, ND, NE, SD)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with
allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Great Plains region including Kansas, North Dakota, Nebraska and South Dakota

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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**Respiratory Syncytial Virus (RSV) Antibodies, IgG and IgM (Separate Determinations), Serum**

**Clinical Information:** Respiratory syncytial virus (RSV) is an important cause of human respiratory infection. It strikes most frequently and severely in the very young and is a common cause of...
bronchiolitis, pneumonia, or croup in young infants. Infections in older children and adults tend to be milder and to involve the upper respiratory tract. RSV infections are seasonal, from late fall to spring, and often occur in epidemic form.

**Useful For:** Aiding in the diagnosis of a recent respiratory syncytial virus infection

**Interpretation:** Normals: -IgG: <1:10 -IgM: <1:10 The presence of IgM class antibodies or a 4-fold or greater rise in paired sera IgG titer indicates recent infection. The presence of demonstrable IgG generally indicates past exposure and immunity.

**Reference Values:**
IgG: <1:10
IgM: <1:10


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**RSVP 800323**

**Respiratory Syncytial Virus (RSV), Molecular Detection, PCR**

**Clinical Information:** Respiratory syncytial virus (RSV) is a respiratory virus that infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults. RSV RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RSV RNA. Nasal swabs have been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA.(1,2) Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

**Useful For:** Rapid and accurate detection of respiratory syncytial virus

**Interpretation:** A positive test result indicates that the patient is presumptively infected with respiratory syncytial virus. The test does not indicate the stage of infection. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis.

**Reference Values:**
Not applicable


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**RETZ 35539**

**RET Proto-Oncogene, Full Gene Analysis**

**Clinical Information:** Mutations in the RET proto-oncogene are associated with 3 distinct, and in rare cases, overlapping clinical syndromes. Multiple endocrine neoplasia type 2 (MEN2): MEN2 is an autosomal dominant cancer syndrome that has classically been divided into 3 subtypes: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). The characteristic features of MEN 2A include multifocal medullary thyroid carcinoma (MTC), bilateral pheochromocytoma, and primary hyperparathyroidism. MEN 2B is characterized by MTC, pheochromocytoma, and multiple mucosal neuromas. Other features of MEN 2B include enlarged nerves of the gastrointestinal tract (ganglioneuromatosis), marfanoid habitus, hypotonia, and corneal nerve thickening. FMTC has
traditionally been diagnosed in families with 4 or more cases of MTC in the absence of pheochromocytoma or parathyroid involvement. Early diagnosis of thyroid cancer and appropriate surgical intervention can prevent metastatic MTC and can reduce the morbidity and mortality associated with MTC. The majority of MEN2-related mutations occur at conserved cysteine residues within exons 10 and 11. Additional mutations in exons 13, 14, 15, and 16 account for the majority of other MEN2-related RET mutations. Taken together, mutations in these codons account for approximately 98% of MEN 2A, >99% of MEN2B, and 96% of FMTC. Hirschsprung disease (HSCR): HSCR is a congenital disorder of impaired intestinal motility, also known as aganglionic megacolon. Variable lengths of the colon may be affected, resulting in either total aganglionosis, long-segment HSCR, or short-segment HSCR. HSCR affects approximately 1 in 5,000 live births and is resolved via surgical intervention. Although gain of function mutations in RET may result in MEN2, loss of function mutations have been reported in patients with Hirschsprung disease (HSCR). It has been reported that up to 50% of familial cases of HSCR and 3% to 35% of sporadic HSCR are due to RET germline mutations. However, most of the mutations that cause HSCR occur outside of the codons that are typically mutated in MEN2. Congenital central hypoventilation syndrome (CCHS): CCHS is a congenital disorder of autonomic nervous system dysfunction in which individuals hypoventilate during sleep, and less commonly while awake. While not the primary etiology of disease, RET mutations have been associated with CCHS; in addition, RET mutations may be modifiers of CCHS development in individuals with HSCR. Co-occurrence of HSCR and CCHS is more commonly observed than the co-occurrence of MEN2 with either HSCR or CCHS.

**Useful For:** Confirmation of suspected clinical diagnosis of multiple endocrine neoplasia type A or B, Hirschsprung disease, or congenital central hypoventilation syndrome in patients with a suspected diagnosis of any of these conditions. Identification of familial RET mutation to allow for predictive or diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**Clinical Information:** Celiac disease (CD) is a genetically inherited autoimmune digestive disease and tends to occur in families of European descent. Family members of people with CD or dermatitis herpetiformis are at increased risk of CD. CD is characterized by a permanent intolerance to gluten. When gluten is ingested, the immune system triggers an isolated inflammatory response in the small intestinal mucosa. A lifetime gluten-free diet can completely stop the immune response. Once the patient is on a gluten-free diet, the small intestine begins to repair itself and the antibody levels decline and eventually disappear. However, reintroduction of gluten-containing products stimulates the immune response again.
A significant reduction in morbidity and mortality occurs when patients adhere to the gluten-free diet. Patients with CD produce various autoantibodies, including endomysial (EMA), tissue transglutaminase (tTG), gliadin, and reticulin antibodies, as part of the immune response. IgA antibodies usually predominate although patients may also produce IgG autoantibodies. The levels of these antibodies decline following institution of a gluten-free diet. tTG is the primary autoantigen recognized by EMA antibodies in patients with CD and is currently considered the most useful first level screening test for CD. Reticulin antibodies are no longer considered useful in the diagnosis of CD because they lack the sensitivity and specificity of the EMA and tTG tests. Serological screening offers a minimally invasive option for rapid identification of those likely to have CD and to select those who should be subjected to biopsy. Markedly positive (serologically) individuals are highly likely to have CD and should undergo biopsy to confirm the diagnosis.

**Useful For:** Investigation of celiac disease (CD) Reticulin antibodies are no longer considered useful in the diagnosis of CD. Mayo Medical Laboratories recommends ordering TTGA / Tissue Transglutaminase (tTG) Antibody, IgA, Serum or EMA / Endomysial Antibodies (IgA), Serum for evaluation of patients suspected of CD or dermatitis herpetiformis.

**Interpretation:** Decreasing titers suggest successful avoidance of gluten.

**Reference Values:**
- Negative
  - If positive, results are titered.

Reference values apply to all ages.

**Clinical References:**

**Reticulocytes, Blood**

**Clinical Information:** Reticulocytes are immature erythrocytes (RBC) that have been released into the peripheral blood from the bone marrow after extrusion of their nucleus. The reticulocyte contains residual polyribosomes used in the formation of hemoglobin in the developing erythrocyte. The reticulocyte count is a measure of the number of RBCs delivered by the bone marrow. It is elevated with active erythropoiesis such as regeneration, and is decreased in hypoplastic or deficiency conditions such as vitamin B12 deficiency.

**Useful For:** Assessing erythropoietic bone marrow activity in anemia and other hematologic conditions

**Interpretation:** Reticulocyte counts must be carefully correlated with other clinical and laboratory findings.

**Reference Values:**
- % Reticulocytes: 0.77-2.36%
- Absolute reticulocytes: 38.1-112.6 x 10^9/L


**Retinol Binding Protein**

**Reference Values:**
- 1.5 - 6.7 mg/dL
Retinol-Binding Protein, 24 Hour, Urine

Clinical Information: Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues. Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubule cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function. Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

Useful For: Assessing renal tubular injury or dysfunction
Screening for other tubular abnormalities
Detecting chronic asymptomatic renal tubular dysfunction

Interpretation: Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

Reference Values:
<163 mcg/24 hours

Clinical References:

Retinol-Binding Protein, Random, Urine

Clinical Information: Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues. Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubule cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function. Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

Useful For: Assessing renal tubular injury or dysfunction
Screening for other tubular abnormalities
Detecting chronic asymptomatic renal tubular dysfunction

Reference Values:
<163 mcg/24 hours
Interpretation: Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

Reference Values:
<50 years: <130 mcg/g creatinine
≥50 years: <172 mcg/g creatinine


**FRHFG 57818**

**Rheumatoid Factor (IgG,IgA,IgM)**

Reference Values:
Rheumatoid Factor (IgG)  
≤6 Negative  
>6 Positive

Rheumatoid Factor (IgA)  
≤6 Negative  
>6 Positive

Rheumatoid Factor (IgM)  
≤6 Negative  
>6 Positive

**RHUT 9060**

**Rheumatoid Factor, Serum**

Clinical Information: Rheumatoid factors (RF) are antibodies that are directed against the Fc fragment of IgG altered in its tertiary structure. Although the IgM class is the most common RF, IgG and IgA RFs have been reported. A variety of tests for the determination of RF have been described including agglutination of sheep erythrocytes which have been sensitized with rabbit IgG, agglutination of polystyrene latex particles which have been coated with human IgG as well as radioimmunoassay and enzyme immunoassays. Over 75% of patients with rheumatoid arthritis (RA) have an IgM antibody to IgG immunoglobulin. This autoantibody (RF) is diagnostically useful although it may not be etiologically related to RA. The titer of RF correlates poorly with disease activity, but those patients with high titers tend to have more severe disease and thus a poorer prognosis than do sero-negative patients. Tests are usually positive for patients with nodules or clinical evidence of vasculitis.

Useful For: Diagnosis and prognosis of rheumatoid arthritis

Interpretation: Positive results are consistent with rheumatoid arthritis.

Reference Values:
<15 IU/mL


**RHNI 82856**

**Rhizopus nigricans, IgE**

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Reference values apply to all ages.**


**FRDG**

**Rhodotorula IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FRUB**

**Rhubarb (Rheum rhaponticum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**RIBAV**

**Ribavirin, Serum**
**Clinical Information:** Ribavirin is a nucleoside analog with antiviral activity against a number of RNA and DNA viruses, including hepatitis C virus (HCV). In combination with interferon, ribavirin is a treatment of choice for chronic HCV infection. In this setting, higher serum concentrations of ribavirin appear to correlate with the likelihood of achieving virological response; however, the drug dose is limited by concentration-dependent hemolytic anemia. Although no consensus therapeutic targets or toxic thresholds have been established, ribavirin concentrations between 2,500 and 4,000 ng/mL have been suggested to improve virological response and minimize toxicity. The half-life of ribavirin is very long, typically 5 days or more. For this reason, steady-state concentrations are not achieved until several weeks into therapy; most studies have performed initial therapeutic monitoring after at least 28 days of ribavirin treatment. Specimens should be drawn immediately prior to the next scheduled dose, or at minimum >12 hours after the last dose. Elimination of ribavirin is also very slow, and due to incorporation of the drug into red blood cells, may take up to 6 months after the cessation of therapy. Ribavirin has shown teratogenic activity in animal models, thus patients are recommended to practice stringent birth control until at least 6 months after the end of treatment.

**Useful For:** Assessing adequacy of ribavirin therapy or potential drug-related toxicity

**Interpretation:** Ribavirin concentrations >2,500 ng/mL appear to correlate with greater likelihood of virological response in patients with chronic hepatitis C virus infection. Elevated concentrations in the setting of hemolytic anemia are consistent with ribavirin toxicity.

**Reference Values:**
2,500-4,000 ng/mL

**Clinical References:**

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**Riboflavin (Vitamin B2), Plasma**

**Clinical Information:** There are 3 principle vitamin B2-active flavins found in nature-riboflavin, riboflavin 5-phosphate (flavin mononucleotide [FMN]), and riboflavin-5’-adenosyl-diphosphate (flavin adenosine dinucleotide [FAD]). In biological tissues, FMN and FAD serve as prosthetic units for a large variety of flavoproteins, which are hydrogen carriers in oxidation-reduction processes. Dietary deficiency of riboflavin (ariboflavinosis) is characterized by sore throat, cheilosis (lesions on the lips), angular stomatitis (lesions on the angles of the mouth), glossitis (fissured and magenta-colored tongue), corneal vascularization, dyssebacia (red, scaly, greasy patches on the nose, eyelids, scrotum, and labia), and normocytic, normochromic anemia. Severe riboflavin deficiency may affect the conversion of vitamin B6 to its coenzyme, as well as conversion of tryptophan to niacin. Riboflavin has a low level of toxicity and no case of riboflavin toxicity in humans has been reported. The limited absorptivity of riboflavin and its ready excretion in the urine normally preclude a health problem due to increased intake of riboflavin.

**Useful For:** Evaluation of persons who present the signs of ariboflavinosis

**Interpretation:** Low concentrations in the blood plasma are indicative of nutritional deficiency. Concentrations <1 mcg/L are considered significantly diminished. Marginally low levels probably represent nutritional deficiency that should be corrected.

**Reference Values:**
Normal: 1-19 mcg/L

**Clinical References:**
Ribosome P Antibodies, IgG, Serum

**Clinical Information:** The 80S mammalian ribosome is composed of approximately equal amounts of protein and RNA. The larger 60S subunit contains 3 acidic phosphoproteins, PO, P1, and P2 with molecular masses of 38 kDa, 19 kDa, and 17 kDa, respectively. The major immunoreactive epitope of these 3 autoantigens is found within 22 consecutive amino acids of the carboxy terminus of these 3 highly conserved proteins. It has been known for some time that sera from some patients with lupus erythematosus (LE) react with ribosomal protein antigens. Studies performed with synthetic peptide antigens revealed that reactivity detected by immunoprecipitation and by immunofluorescence methods in sera from LE patients was directed at the above mentioned epitope. Antibodies to ribosome P proteins are considered highly specific for LE, and have been reported in patients with central nervous system (CNS) involvement and so called "lupus psychosis." The reported frequency of antibodies to ribosome P protein autoantigens in patients with LE is approximately 12%. Since patients with LE may manifest signs and symptoms of CNS diseases including neuropsychiatric symptoms, the presence of antibodies to ribosome P protein may be useful in the differential diagnosis of such patients. Other causes of CNS symptoms in patients with LE include thrombosis with or without antibodies to phospholipid antigens and iatrogenic effects from treatment with corticosteroid drugs.

**Useful For:** As an adjunct in the evaluation of patients with lupus erythematosus (LE) As an aid in the differential diagnosis of neuropsychiatric symptoms in patients with LE

**Interpretation:** A positive result is consistent with the diagnosis of lupus erythematosus, and may indicate the presence of central nervous system involvement.

**Reference Values:**
- <1.0 U (negative)
- > or =1.0 U (positive)
Reference values apply to all ages.

**Clinical References:**

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Rice IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
- <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Rice, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Rickettsial Disease Panel**

**Reference Values:**

- R. Typhi IgG/IgM
- RMSF IgG/IgM

**Reference Range:** Not Detected

- Q Fever IgG/IgM Phase I/II Screens

**Reference Range:** Negative
Q Fever Antibody testing includes differentiation of antibodies to Phase I and Phase II antigenic variants. Coxiella burnetii, which causes Q Fever, undergoes transitions between Phase I and Phase II states. These phases are serologically distinguishable and useful in the serodiagnosis of acute and chronic disease.

In some cases, the ratio of titer of phase II to phase I may indicate the stage of the disease. A ratio of greater than 1 may indicate the acute stage; greater than or equal to 1, granulomatous hepatitis; and less than 1, the chronic stage or endocarditis.

As with other infectious diseases, IgM antibodies are the first to appear. Usually they are detectable for a few weeks or, at the most, for a few months. IgG antibodies appear somewhat later but can persist for years, even for life.

Although single phase II IgG titers of 1:256 or greater are considered evidence of acute C. burnetii disease, the best criterion for a dependable diagnosis is still the demonstration of a fourfold or higher increase in antibody titer between the acute and convalescent serum samples.

**FRISP**

*Risperidone (Risperdal) and 9-Hydroxyrisperidone*

**Reference Values:**

Units: ng/mL

Expected steady state concentrations of risperidone and 9-hydroxyrisperidone (combined total) in patients receiving recommended daily dosages: 10 - 120 ng/mL.

**RIAS**

*Ristocetin Inhibitor Assay Screen, Plasma*

**Clinical Information:** Inhibitors of the von Willebrand factor (VWF) may occur in those patients with severe type 3 von Willebrand's disease (VWD) who have a deletion of a large part of the von Willebrand gene. Inhibitors may also occur in patients who have no previous evidence of VWD resulting in the development of a form of acquired VWD. Only a few of the patients with acquired VWD have evidence of an inhibitor. Most patients with acquired VWD have some type of B-cell lymphocytic abnormality (hairy cell leukemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, multiple myeloma, monoclonal gammopathy of undetermined significance, Waldenstrom's macroglobulinemia, and systemic lupus erythematosus). Other patients with acquired VWD may have some form of myeloproliferative disease. Acquired VWD rarely arises in a person who is otherwise healthy. Most inhibitors of VWF are IgG, but occasionally IgM and IgA have been reported. Inhibiting antibodies to VWF are measured by determining the degree of inhibition of ristocetin/VWF-induced agglutination of washed normal platelets.

**Useful For:** Diagnosis of inhibitors of von Willebrand factor in patients with severe (type 3) von Willebrand disease (VWD) Diagnosis of certain acquired types of VWD

**Interpretation:** An interpretive report is issued. Inhibitors may also occur in patients with severe type 3 von Willebrand disease. Unlike the acquired form of the disease, these latter patients will have a history of lifelong recurrent bleeding.

**Reference Values:**

An interpretive report will be provided.

RNA Polymerase III Antibodies, IgG, Serum

Clinical Information: Systemic sclerosis is a multisystem connective tissue (systemic rheumatic) disease characterized by fibroblast dysfunction leading to fibrosis of the skin and internal organs, microvascular injury leading to tissue hypoxia, and an autoimmune response manifested by production of autoantibodies.(1,2) The severity of the disease is highly variable among individual patients. Limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis have been recognized as distinct subsets, with worse survival for those with the diffuse form.(2) Clinical features of CREST syndrome (calcinosi sis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) can be seen in both limited cutaneous and diffuse cutaneous forms but, overall, are associated with a better prognosis.(2) Several disease-specific and mutually exclusive autoantibodies have been identified that are helpful in both diagnosis and disease classification. Centromere and topoisomerase I (Scl 70) autoantibodies are associated with limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis, respectively.(3) Nucleolar antibodies have been found in 11% to 23% of patients with systemic sclerosis.(1,4) Systemic sclerosis patients who are positive for nucleolar antibodies form a distinct serologic subgroup and usually do not have any of the other antibodies typically found in systemic sclerosis patients such as anticentromere or anti-Scl70.(1) Numerous studies have shown that systemic sclerosis patients with anti-nucleolar antibodies have an increased risk of the diffuse form of scleroderma, with a high likelihood of skin involvement and hypertensive renal disease.(1,4)

Useful For: Evaluating patients suspected of having systemic sclerosis, when used in conjunction with centromere and Scl70 antibodies Providing diagnostic and prognostic information in patients with systemic sclerosis

Interpretation: A positive result supports a possible diagnosis of systemic sclerosis (see Cautions). This autoantibody is strongly associated with diffuse cutaneous scleroderma and with an increased risk of acute renal crisis. A negative result indicates no detectable IgG antibodies to RNA polymerase III, but does not rule out the possibility of systemic sclerosis (11%-23% sensitivity).(1,4)

Reference Values:
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-80.0 U (moderate positive)
>80.0 U (strong positive)


RNP Antibodies, IgG, Serum

Clinical Information: RNP (also called nRNP and U1RNP) is a small nuclear ribonucleoprotein that contains 3 protein autoantigens (called A, C, and 68 kD). Sera that contain RNP antibodies react predominately with the A and 68 kD autoantigens. Antibodies to RNP occur in approximately 50% of patients with lupus erythematosus (LE) and in patients with other connective tissue diseases, notably mixed connective tissue disease (MCTD). MCTD is characterized by high levels of RNP antibodies without detectable Sm or double-stranded DNA (dsDNA) antibodies. MCTD resembles LE but is not accompanied by renal involvement.(1,2) RNP is 1 of 4 autoantigens commonly referred to as extractable
nuclear antigens (ENA). The other ENAs are SS-A/Ro, SS-B/La, and Sm. Each ENA is composed of 1 or more proteins associated with small nuclear RNA species (snRNP) ranging in size from 80 to approximately 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, MCTD, Sjogren's syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive result for RNP antibodies is consistent with a connective tissue disease. Although strongly associated with connective tissue diseases, RNP antibodies are not considered a "marker" for any particular disease except in the following situation: when found in isolation (ie, dsDNA antibodies and Sm antibodies are not detectable), a positive result for RNP antibodies is consistent with the diagnosis of mixed connective tissue disease.

**Reference Values:**

- <1.0 U (negative)
- > or =1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


**ROMA (Risk of Ovarian Malignancy Algorithm)**

**Interpretation:** The Risk of Ovarian Malignancy Algorithm (Roma) test is intended to aid in assessing the risk of ovarian cancer in women with a pelvic mass based on the patient's HE4 and CA125 levels, and their menopausal status. Women with ROMA levels above the cutoff have an increased risk of ovarian cancer. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment.

**Reference Values:**

- ROMA Premenopausal  <1.31
- ROMA Postmenopausal <2.77
- CA125  <35 U/mL
- HE4  <151 pM

**Ropivacaine, Serum/Plasma**

**Reference Values:**

Reporting limit determined each analysis.

Following epidural administration 10 mg/hr, 20 mg/hr and 30 mg/hr, mean plasma concentration of 0.39, 0.88, 1.19 mcg/mL at 21 hours respectively.

Bolus I.V. administration 84 mg/70 kg and 131 mg/70 kg, peak plasma concentrations of 1.1 and 1.7 mcg/mL at 2 minutes respectively.
**Rosemary (Rosmarinus officinalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Rotavirus Antigen, Feces**

**Clinical Information:** Rotavirus is a major cause of nonbacterial gastroenteritis, especially in infants and very young children (6 months–2 years of age). Infection may be entirely asymptomatic or produce a spectrum of disease ranging from mild gastroenteritis to severe diarrhea and vomiting with dehydration. Infection usually begins acutely and lasts for 4 to 8 days. In temperate climates, rotaviral infections are seasonal; they peak in frequency during the winter months and are uncommon during the summer. Rotaviral gastroenteritis is, therefore, sometimes called "winter vomiting disease." Infection is more likely to be symptomatic in preterm infants, immunosuppressed patients and elderly individuals, especially those living in nursing homes or other confined quarters. In other children and adults, rotavirus infections are usually subclinical and may be associated with asymptomatic shedding of rotavirus in the feces. Rapid and accurate detection of rotavirus antigens in stool specimens may lead to better patient management, particularly in hospitalized or institutionalized patients.

**Useful For:** Investigation of patients with diarrhea, particularly infants, the elderly, and immunocompromised patients Investigation of nosocomial diarrhea

**Interpretation:** Peak viral counts are reported to occur on days 3 to 5 after onset of symptoms. The virus is eliminated from the infected individual within a few days following acute infection. Specimens collected 8 days or more after onset of symptoms may not contain enough rotavirus antigen to produce a positive reaction. A prolonged carrier state has been recognized with rotavirus infection. The rate of positive test results may vary due to age, weather, seasonal factors, geographic location, and the general health environment for the group under study. See Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Reference Values:**
Negative


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**Rough Marsh Elder, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**RRRP 82723 Rough Pigweed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Rubella Antibodies, IgG, Serum

Clinical Information: Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. Primary, in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, cardiovascular and ocular defects. The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. A total of 4 cases of rubella were reported to the CDC in 2011 without any cases of congenital rubella syndrome. Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (cdc.gov/rubella). However, immunity may wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella.

Useful For: Determination of immune status to the rubella virus

Interpretation: Positive: Antibody index (AI) value > or =1.0 - The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cut-off for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. - The presence of detectable IgG-class antibodies indicates immunity to the rubella virus through prior immunization or exposure. Individuals testing positive are considered immune to rubella infection. Equivocal: AI value 0.8-0.9 - Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value < or =0.7 - The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the rubella virus.

Reference Values:
Vaccinated: positive (> or =1.0 AI)
Unvaccinated: negative (< or =0.7 AI)

cause of death where nutrition and sanitation are limited. Onset begins with cough, fever, and lymphadenopathy approximately 2 weeks after exposure. Diagnosis is usually made when the rash appears. Koplik’s spots may be seen earlier on the buccal mucosa. Complications of measles may develop in children who appear to have normal immune functions. Persistent infection of the central nervous system with measles virus is recognized to cause the disease subacute sclerosing panencephalitis (SSPE). SSPE is a rare, late complication of measles with an incidence of approximately 1 per 100,000 cases. SSPE is a progressive, usually fatal disease that occurs most often in children between the ages of 5 and 14. The onset is insidious and progressive. The incubation period from acute measles to onset of neurological symptoms varies from several months to many years. One of the most useful diagnostic tests involves the measurement of measles-specific antibodies in the cerebrospinal fluid (CSF) of patients with SSPE. Levels of antibody are significantly elevated in the CSF of SSPE patients compared to those without the disease.

**Useful For:** Diagnosis of central nervous system infection with rubeola (measles) virus and/or subacute sclerosing panencephalitis

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection. Patients with subacute sclerosing panencephalitis have serum antibody titers which are 10 to 100 times higher than those seen in late convalescent-phase sera. More importantly, there is pronounced local production of oligoclonal measles virus antibodies in the central nervous system. Normals: -IgG: <1:5 -IgM: <1:10

**Reference Values:**

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**Clinical References:** Gascon GG: Subacute sclerosing panencephalitis. Semin Pediatr Neurol 1996;3:260-269

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**Rufinamide, Serum**

**Clinical Information:** Rufinamide is a new antiepileptic drug (AED) approved by the Food and Drug Administration as add-on treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children > or =4 years, and for the treatment of focal seizures in adults and adolescents. Its mechanism of action is not completely understood, but it is believed to work by prolonging the inactive state of sodium channels and therefore limiting excessive firing of sodium-dependent action potentials. The most commonly observed side effects are headache, dizziness, fatigue, somnolence, and nausea.

**Useful For:** Monitoring serum rufinamide concentrations, assessing compliance, and adjusting dosage in patients receiving other drugs which interact pharmacokinetically with rufinamide (ie, drugs that induce liver CYP3A4 enzymes) and may be helpful in who are receiving hemodialysis

**Interpretation:** The reference interval is broad and represents the concentrations observed to be associated with the greatest drug efficacy without side effects or toxicity.

**Reference Values:**

5.0-30.0 mcg/mL

**Russian Thistle, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>


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**Rye Food IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantiation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Rye Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Rye, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
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Reference values apply to all ages.


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**S-100B Protein, Serum**

**Reference Values:**

0 â€“ 96 ng/L

This assay is performed using the CanAg S100 Enzyme Immunoassay. Results obtained with different assay methods or kits cannot be used interchangeably.

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**Saccharomyces cerevisiae Antibody, IgA, Serum**

**Clinical Information:** Inflammatory bowel disease (IBD) refers to 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD), that produce inflammation of the large or small intestines. (1) The diagnoses of both diseases are based on clinical features, the results of barium X-rays, colonoscopy, mucosal biopsy histology, and in some cases operative findings and resected bowel pathology and histology. Recently, patients with IBD have been shown to have antibodies in serum that help distinguish between CD and UC. (2) Patients with UC often have measurable neutrophil-specific antibodies, which react with as yet uncharacterized target antigens in human neutrophils; whereas, patients with CD often have measurable antibodies of the IgA and/or IgG isotypes, which react with cell wall mannan of Saccharomyces cerevisiae strain Su 1.

**Useful For:** Helping clinicians distinguish between ulcerative colitis and Crohn's disease in patients suspected of having inflammatory bowel disease.

**Interpretation:** In IBDP / Inflammatory Bowel Disease Serology Panel, Serum, anti-Saccharomyces
Saccharomyces cerevisiae Antibody, IgG, Serum

GASCA

83023

Clinical Information: Inflammatory bowel disease (IBD) refers to 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD), which produce inflammation of the large or small intestines. The diagnoses of both diseases are based on clinical features, radiographic findings, colonoscopy, mucosal biopsy, and, in some cases, operative findings and resected bowel pathology. Patients with IBD have also been shown to have antibodies in serum that help distinguish between CD and UC. Patients with UC often have measurable neutrophil-specific antibodies (NSA) that react with as yet uncharacterized target antigens in human neutrophils; whereas patients with CD often have measurable antibodies of the IgA and/or IgG isotypes that react with cell wall mannan of Saccharomyces cerevisiae strain Su 1.

Useful For: Helping clinicians distinguish between ulcerative colitis and Crohn's disease in patients suspected of having inflammatory bowel disease.

Interpretation: In IBDP / Inflammatory Bowel Disease Serology Panel, Serum, anti-Saccharomyces cerevisiae antibodies (ASCA) and neutrophil-specific antibodies (NSA) are measured. The finding of NSA with normal levels of IgA and IgG ASCA is consistent with the diagnosis of ulcerative colitis (UC); the finding of negative NSA with elevated IgA and IgG ASCA is consistent with Crohn's disease (CD). NSA are detectable in approximately 50% of patients with UC. Elevated levels of either IgA or IgG ASCA occur in approximately 55% of patients with CD. Approximately 40% of patients with CD have elevated levels of both IgA and IgG ASCA. Employed together, the tests for NSA and ASCA have the following positive predictive values (PPV) for UC and CD, respectively: (2) - NSA-positive with normal levels of IgA and IgG ASCA, PPV of 91% - NSA-negative with elevated levels of IgA and IgG ASCA, PPV of 90%.

Reference Values:
Negative: < or =20.0 U
Equivocal: 20.1-24.9 U
Weakly positive: 25.0-34.9 U
Positive: > or =35.0 U
Reference values apply to all ages.


**FSFLE 57541**

**Safflower (Carthamus tinctorius) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FSAG 57957**

**Sage (Artemisia spp.) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FSGFE 57565**

**Sage (Salvia officinalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10–0.34 Equivocal 1 0.35–0.69 Low Positive 2 0.70–3.4 Moderate Positive 3 3.5–17.4 High Positive 4 17.5–49.9 Very High Positive 5 50.0–99.9 Very High Positive 6 >=100 Very High Positive

**Reference Values:**

<0.35 kU/L

**SALCA 37061**

**Salicylate, Serum**

**Clinical Information:** Therapeutic salicylates include, among others, salicylic acid, sodium salicylate, methyl salicylate (oil of wintergreen), and acetylsalicylic acid (aspirin). Aspirin is an analgesic, antipyretic, anti-inflammatory drug contained in a large number of preparations. Aspirin is rapidly hydrolyzed by hepatic and blood esterases to the pharmacologically active intermediate, salicylic acid, which has a dose-dependent serum half-life ranging from 3 to 20 hours. Stimulation of the respiratory center in the central nervous system and uncoupling of oxidative phosphorylation are direct effects of salicylate that lead to many of the toxic symptoms observed in overdose situations. Symptoms of salicylate toxicity can include nausea, vomiting, tinnitus, headache, hyperpnea, confusion, hyperthermia, slurred speech, and convulsions. Acid-base disturbances such as compensated respiratory alkalosis (mild toxicity) and metabolic acidosis with increased anion gap (severe toxicity) are commonplace.

**Useful For:** Assessing toxicity This test is not useful for assessing low-dose aspirin therapy

**Interpretation:** Therapeutic concentrations for antipyretic/analgesic are 3.0 to 10.0 mg/dL, while concentrations between 1.5 and 30 mg/dL are for anti-inflammatory/rheumatic fever. Toxic concentrations are > or =50.0 mg/dL.

**Reference Values:**

Therapeutic: <30.0 mg/dL

Critical value: > or =50.0 mg/dL

Salmon IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Salmon, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Salmonella Antibodies, EIA

Reference Values:
Reference Range: Negative

Antibodies to Salmonella flagellar (H) and somatic (O) antigens typically peak 3-5 weeks after infection. A positive result in this assay is equivalent to a titer of $\geq 1:160$ by tube agglutination (Widal). Results should not be considered as diagnostic unless confirmed by culture.

Salt Grass, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Sardine (Pilchard), IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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FSCA6  91586  SCA 6 (CACNA1A) Repeat Expansion

Reference Values: A final report will be attached in MayoAccess.

FSCA1  91585  SCA1 (ATXN1) Repeat Expansion

Reference Values: A final report will be attached in MayoAccess.
SCA3 (MJC/ATXN3) Repeat Expansion

Reference Values:
A final report will be attached in MayoAccess.

Scale, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Schistosoma Exam, Urine**

**Clinical Information:** Schistosomiasis is an infection caused by several species of trematodes (flukes) in the genus Schistosoma. The adult worms of Schistosoma hematobium inhabit the venus plexus of the bladder and rectum and produce eggs which are typically passed in the urine. Identification of characteristic eggs in urine is diagnostic for infection with this organism.

**Useful For:** As an aid in diagnosing schistosomiasis infections involving the urinary tract

**Interpretation:** A positive result indicates the presence of Schistosoma species ova in urine. A negative result does not rule out the presence of Schistosoma species since ova may be present at levels below the detection limits of this assay, or infection may not involve the urinary tract.

**Reference Values:**

| If positive, organism identified |

**Schistosoma IgG Antibody, FMI (Serum)**

**Reference Values:**

REFERENCE RANGE: <1.00

**INTERPRETIVE CRITERIA:**

- <1.00 Antibody Not Detected
- > or = 1.00 Antibody Detected

This assay utilizes the microsomal fraction of adult *S. mansoni* worms (MAMA) as antigen, and is thus highly specific (99%) and sensitive (96%) for detection of infection caused by *S. mansoni*. Although the assay is also highly specific for infections caused by other *Schistosoma* species (*S. japonicum*, *S. haematobium*, *S. mekongi*), its sensitivity for these infections is lower (55%). Antibody levels do not correlate with intensity of infection.

**Scl 70 Antibodies, IgG, Serum**

**Clinical Information:** Scl 70 (topoisomerase 1) is a 100-kD nuclear and nucleolar enzyme. Scl 70 antibodies are considered to be specific for scleroderma (systemic sclerosis) and are found in up to 60% of patients with this connective tissue disease. Scl 70 antibodies are more common in patients with extensive cutaneous involvement and interstitial pulmonary fibrosis, and are considered a poor prognostic sign. (1, 2)

See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients with signs and symptoms of scleroderma and other connective tissue diseases in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive test result for Scl 70 antibodies is consistent with a diagnosis of scleroderma.

**Reference Values:**

- <1.0 U (negative)
- > or =1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


**SDHB Gene, Full Gene Analysis**

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germ line copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce...
catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternaly transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NFI (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted presymptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHB gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

SDHP

SDHB, SDHC, SDHD Gene Panel

Clinical Information: Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDH shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical
utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with SDHB, SDHC, and SDHD gene mutations

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**SDHCZ 37443**

**SDHC Gene, Full Gene Analysis**

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants).
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**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHC gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

SDHD Gene, Full Gene Analysis

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting paternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for.
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**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHD gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Seafood Allergen Profile**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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Reference values apply to all ages.


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**SEAS 31766**

**Seasonal Inhalants Allergen Profile**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>4</td>
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</tbody>
</table>
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


### SECOS 8243

**Secobarbital, Serum**

**Clinical Information:** Secobarbital is a short-acting barbiturate with hypnotic properties used as a preanesthetic agent and in the short-term treatment of insomnia. Secobarbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a volume of distribution (Vd) of 1.6 to 1.9 L/kg, and about 46% to 70% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. Secobarbital's half-life is about 15 to 40 hours (mean: 28 hours).

**Useful For:** Monitoring secobarbital therapy

**Interpretation:** Therapeutic concentration: 1.0 to 2.0 mcg/mL  Toxid concentration: >5.0 mcg/mL

**Reference Values:**
- Therapeutic concentration: 1.0-2.0 mcg/mL
- Toxic concentration: >5.0 mcg/mL

Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

**Clinical References:**

### FSEC 90173

**Secretin**

**Clinical Information:** Secretin is a 27 amino acid basic peptide produced by S cells and released by acid delivered into the duodenum. Secretin is released into the blood when duodenal pH drops below 4. Secretin shares structural similarity with Glucagon, Gastric Inhibitory Polypeptide, Vasoactive Intestinal Polypeptide, PHIM, and Growth Hormone- Releasing Hormone. Secretin is a potent stimulus for bicarbonate secretion. Secretin also stimulates secretion of bile, release of Insulin, and release of Gastric Pepsin in the stomach. Secretin inhibits Glucagon release, intestinal motility, and prevents the uptake of water and sodium ions by the intestine. In normal patients, Secretin has little effect on Gastrin levels, but stimulates Gastrin greatly in Zollinger-Ellison patients. Secretin is also elevated in Zollinger-Ellison patients and in patients with duodenal ulcer. Secretin levels are low in patients with pernicious anemia and achlorhydria. Secretin secretion can be suppressed by Somatostatin, Cimetidine, and Methionine-Enkephalin.

**Reference Values:**
12 - 75 pg/mL (mean=25)

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.
Reference Values:
The following threshold concentrations are used for this analysis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening Threshold</th>
<th>Confirmation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Alcohol</td>
<td>0.020 gm/dL</td>
<td>0.020 gm/dL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>300 ng/mL</td>
<td>100 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>100 ng/mL</td>
<td>75 ng/mL</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>100 ng/mL</td>
<td>300 ng/mL</td>
</tr>
</tbody>
</table>

Ketamine: Negative
Screening threshold: 100 ng/mL

Gamma-Hydroxybutyric Acid (GHB): Negative
Screening threshold: 5.0 ug/mL

Selenium, Serum

Clinical Information: Selenium is an essential element. It is a cofactor required to maintain activity of glutathione peroxidase (GSH-Px), an enzyme that catalyzes the degradation of organic hydroperoxides. The absence of selenium correlates with loss of GSH-Px activity and is associated with damage to cell membranes due to accumulation of free radicals. The normal daily dietary intake of selenium is 0.01 to 0.04 parts per million (ppm), which is similar to the typical content of soil (0.05 ppm) and sea water (0.09 ppm). Selenium is found in many over-the-counter vitamin preparations because its antioxidant activity is thought to be anticarcinogenic. There is no supporting evidence that selenium suppresses cancer. In humans, cardiac muscle is the most susceptible to selenium deficiency. With cell membrane damage, normal cells are replaced by fibroblasts. This condition is known as cardiomyopathy and is characterized by an enlarged heart whose muscle is largely replaced by fibrous tissue. In the United States, selenium deficiency is related to use of total parenteral nutrition. This is therapy administered to patients with no functional bowel, such as after surgical removal of the small and large intestine because of cancer, or because of acute inflammatory bowel disease such as Crohn’s disease. Selenium supplementation to raise serum concentration >70 ng/mL is the usual treatment. Serum monitoring done on a semiannual basis checks the adequacy of supplementation. Selenium toxicity has been observed in animals when daily intake exceeds 4 ppm. Teratogenic effects are frequently noted in the offspring of animals living in regions where soil content is high in selenium such as south-central South Dakota and northern-coastal regions of California. Selenium toxicity in humans is not known to be a significant problem except in acute overdose cases. Selenium is not classified as a human teratogen.

Useful For: Monitoring selenium replacement therapy

Interpretation: Selenium accumulates in biological tissue. The normal concentration in adult human blood serum is 70 to 150 ng/mL (0.15 parts per million) with a population mean value of 98 ng/mL. Optimal selenium concentration is age dependent (see Reference Values); children require less circulating selenium than do adults. In the state of selenium deficiency associated with loss of glutathione peroxidase activity, the serum concentration is usually <40 ng/mL.

Reference Values:
0-2 months: 45-90 ng/mL
3-6 months: 50-120 ng/mL
7-9 months: 60-120 ng/mL
10-12 months: 70-130 ng/mL
>1 year: 70-150 ng/mL

Semen Analysis

Clinical Information: Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid.

Useful For: Determining male fertility status

Interpretation: Semen specimens can vary widely in the same man from specimen to specimen. Semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient's fertility status.

Reference Values:
Appearance: normal
Volume: > or =1.5 mL
pH: > or =7.2
Motile/mL: > or =6.0 x 10(6)
Sperm/mL: > or =15.0 x 10(6)
Motility: > or =40%
Grade: > or =2.5

Note: Multiple laboratory studies have indicated that semen parameters for motility and grade on average retain 80% of original parameters when our shipping method is used for transport. Using these averages, samples with 32% to 39% motility and grade of 2 may be in the normal range if testing was performed shortly after collection. Therefore, these borderline patients may need to collect another sample at a local fertility center to verify fertility status. Motile/ejaculate: > or =9.0 x 10(6)
Viscosity: > or =3.0
Agglutination: > or =3.0
Supravital: > or =58% live
Fructose: positive

Note: Fructose testing cannot be performed on semen analysis specimens shipped through Mayo Medical Laboratories. If patient is azoospermic, refer to FROS / Fructose, Semen or Seminal Plasma. Submit separate specimen to rule out ejaculatory duct blockage. Positive result indicates no blockage.

Semen Analysis with Strict Morphology

Clinical Information: Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid. One of the more successful treatments for male and/or female infertility is in vitro fertilization (IVF). Male partners are tested with the strict criteria sperm morphology test prior to IVF to assist in the diagnosis of male-factor defects. Abnormalities in sperm morphology are related to: defects in sperm transport, sperm capacitation, the acrosome reaction, binding and penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple's IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best
chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).

**Useful For:** Determining male fertility status Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

**Interpretation:** Semen specimens can vary widely in the same man from specimen to specimen. semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patientâ€™s fertility status. Sperm are categorized according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

**Reference Values:**

**SEMEN ANALYSIS**

<table>
<thead>
<tr>
<th>Appearance: normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume: &gt; or =1.5 mL</td>
</tr>
<tr>
<td>pH: &gt; or =7.2</td>
</tr>
<tr>
<td>Motile/mL: &gt; or =6.0 x 10(6)</td>
</tr>
<tr>
<td>Sperm/mL: &gt; or =15.0 x 10(6)</td>
</tr>
<tr>
<td>Motility: &gt; or =40%</td>
</tr>
<tr>
<td>Grade: &gt; or =2.5</td>
</tr>
</tbody>
</table>

**STRICT MORPHOLOGY**

| Normal forms: > or =4.5% normal oval sperm heads |
| Germ cells: <4 x 10(6) (normal) |
| > or =4 x 10(6)/mL (elevated germinal cells in semen are of unknown clinical significance) |
| WBC: <1 x 10(6) (normal) |
| > or =1 x 10(6)/mL (elevated white blood cells in semen are of questionable clinical significance) |


**Seminal Fluid, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat...
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;  or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**MIC 801659**

**Sensitivity, MIC (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**FSMN 91449**

**SensoriMotor Neuropathy Evaluation-Complete**

**Reference Values:**

A final report will be attached in MayoAccess.

**SEPTZ 35548**

**SEPT9 Gene, Mutation Screen**

**Clinical Information:** Hereditary neuralgic amyotrophy (HNA) is an autosomal dominant disorder characterized by periods of severe pain involving the brachial plexus followed by muscle atrophy and weakness. These recurrent episodes can also be accompanied by decreased sensation and paresthesias. Individuals with this disease are generally symptom-free between pain attacks, though many experience lingering effects with repeated attacks. The pain episodes are frequently triggered by physical, emotional, or immunological stress. Less commonly, affected individuals can exhibit nonneurological features including short stature, skin folds, hypotelorism, and cleft palate. Mutations in the SEPT9 gene cause the clinical manifestations of HNA. There are 3 common mutations that have been reported in affected individuals: c.-134G->C, p.R88W, and p.S93F. Additionally, a common exonic duplication attributed to
the founder effect has been identified in North American HNA families. Other private duplications of varying sizes have also been identified in affected individuals. SEPT9 is currently the only known gene associated with HNA, although approximately 15% of HNA families do not show linkage to this gene.

**Useful For:** Confirmation of a diagnosis of hereditary neuralgic amyotrophy

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Sequential Maternal Screening, Part 1, Serum**

**Clinical Information:** Maternal serum screening has historically been used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects, such as Down syndrome and trisomy 18. Screening in the second trimester has been available in some version (i.e., alpha fetoprotein [AFP] test, triple screen, quad screen) for decades. Screening in the first trimester became an established alternative over the last decade. More recently, sequential screening, which has an improved detection rate as compared to either first- or second-trimester screening, has become a standard option. Sequential screening has a higher detection rate because information about a pregnancy is collected in both trimesters, which provides a greater opportunity for detecting problems. Sequential Maternal Screening, Part 1, Serum involves an ultrasound and a blood draw. The ultrasound measurement is of the back of the fetal neck, where fluid tends to accumulate in babies who have chromosome conditions, heart conditions, and other health problems. The measurement, referred to as the nuchal translucency (NT), is difficult to perform accurately. Therefore, NT data is accepted only from NT-certified sonographers. Along with the NT measurement, a maternal serum specimen is drawn and 1 pregnancy-related marker is measured (pregnancy-associated plasma protein A: PAPP-A). The results of the ultrasound measurement and blood work are then entered, along with the maternal age and demographic information, into a mathematical model that calculates Down syndrome and trisomy 18 risk estimates. If the result from the first-trimester screening is positive, the patient is typically offered counseling and diagnostic testing (i.e., chorionic villus sampling or amniocentesis). The screen is completed after Sequential Maternal Screen Part 1, a neural tube defect (NTD) risk is not provided. For a stand-alone NTD-risk assessment, order MAFP / Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum. If the risk from the first trimester is below the established cutoff, an additional serum specimen is drawn in the second trimester for Sequential Maternal Screen, Part 2, which includes tests for AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A. Once that specimen is processed, information from both trimesters is combined and a report is issued. If results are positive, the patient is typically offered counseling and diagnostic testing (i.e., amniocentesis). Nuchal Translucency (NT): The NT measurement, an ultrasound marker, is obtained by measuring the fluid-filled space within the nuchal region (back of the neck) of the fetus. While fetal NT measurements obtained by ultrasonography increase in normal pregnancies with advancing gestational age, fetuses with Down syndrome have larger NT measurements than gestational age-matched normal fetuses. Increased fetal NT measurements can, therefore, serve as an indicator of an increased risk for Down syndrome.

**Pregnancy-Associated Plasma Protein A (PAPP-A):** PAPP-A is a 187-kDa protein comprised of 4 subunits: 2 PAPP-A subunits and 2 pro-major basic protein (proMBP) subunits. PAPP-A is a...
metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4), dramatically reducing IGFBP-4 affinity for IGF1 and IGF2, thereby regulating the availability of these growth factors at the tissue level. PAPP-A is highly expressed in first-trimester trophoblasts, participating in regulation of fetal growth. Levels in maternal serum increase throughout pregnancy. Low PAPP-A levels before the fourteenth week of gestation are associated with an increased risk for Down syndrome and trisomy 18.

**Useful For:** Prenatal screening for Down syndrome and trisomy 18 Prenatal screening for neural tube defects (this is only applicable to Part 2 [second trimester] of the test)

**Interpretation:** Maternal screens provide an estimation of risk, not a diagnosis. A negative result indicates that the estimated risk falls below the screen cutoff. A positive result indicates that the estimated risk exceeds the screen cutoff. Down Syndrome: Sequential Maternal Screening, Part 1, Serum results are negative when the calculated risk is below 1/50 (2%). If Part 1 is negative, submit an additional specimen in the second trimester (order SEQF / Sequential Maternal Screening, Part 2, Serum). Sequential Maternal Screening, Part 2, Serum results are negative when the calculated risk is below 1/270 (0.37%). Negative results mean that the risk is less than the established cutoff; they do not guarantee the absence of Down syndrome. Results are positive when the risk is greater than the established cutoff (ie, > or =1/50 in Sequential Maternal Screening, Part 1, Serum and > or =1/270 in Sequential Maternal Screening, Part 2, Serum). Positive results are not diagnostic. When both Sequential Maternal Screening Part 1 and Part 2 are performed with a screen cutoff of 1/270, the combination of maternal age, nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 90% with a false-positive rate of approximately 3% to 4%. In practice, both the detection rate and false-positive rate vary with maternal age. Trisomy 18: In Part 1, trisomy 18 results are only reported if the Down syndrome risk is positive. In Part 2, the screen cutoff for trisomy 18 is 1 in 100 (1%). Risks that are > or =1% are screen-positive; positive results are not diagnostic. Risks <1% are screen-negative; negative results do not guarantee the absence of trisomy 18. Use caution when revising positive results with earlier dating. Babies with trisomy 18 tend to be small, which can lead to underestimation of gestational age and an increased chance of missing a true-positive. When both Sequential Maternal Screening Part 1 and Part 2 of sequential screening are performed with a screen cutoff of 1/100, the combination of maternal age, PAPP-A, AFP, uE3, and hCG has an overall detection rate of approximately 90% with a false-positive rate of approximately 0.1%. Neural Tube Defect (NTD): Risk assessment for NTD is only available after completion of Part 2 of the sequential maternal screen. See SEQF / Sequential Maternal Screening, Part 2, Serum for details. Follow-up: Verify that all information used in the risk calculation is correct (maternal date of birth, gestational dating, etc). If any information is erroneous, contact the laboratory for a revision. Screen-negative results typically do not warrant further evaluation. If the results are positive, the patient is typically offered counseling, ultrasound, diagnostic testing, and possibly, referral to genetics counseling or a high-risk clinic.

**Reference Values:**
An interpretive report will be provided. See Interpretation section for more details.

**Clinical References:**

**Sequential Maternal Screening, Part 2, Serum**

**Clinical Information:** Maternal serum screening has historically been used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects, such as Down syndrome and trisomy 18. Screening in the second trimester has been available in some version (eg, alpha fetoprotein [AFP] test, triple screen, quad screen) for decades. Screening in the first trimester became an established
alternative over the last decade. More recently, sequential screening, which has an improved detection rate as compared to either first- or second-trimester screening, has become a standard option. Sequential screening has a higher detection rate because information about a pregnancy is collected in both trimesters, which provides a greater opportunity for detecting problems. Sequential Maternal Screening, Part 1, Serum involves an ultrasound and a blood draw. The ultrasound measurement is of the back of the fetal neck, where fluid tends to accumulate in babies who have chromosome conditions, heart conditions, and other health problems. This measurement, referred to as the nuchal translucency (NT), is difficult to perform accurately. Therefore, NT data is accepted only from NT-certified sonographers. Along with the NT measurement, a maternal serum specimen is drawn and 1 pregnancy-related marker is measured (pregnancy-associated plasma protein A: PAPP-A). The results of the ultrasound measurement and blood work are then entered with the maternal age and demographic information into a mathematical model that calculates Down syndrome and trisomy 18 risk estimates. If the result from Part 1 indicates a risk for Down syndrome that is higher than the screen cutoff, the screen is completed and a report is issued. In that event, the patient is typically offered counseling and diagnostic testing (either chorionic villus sampling or amniocentesis). When the screen is completed after Sequential Maternal Screening Part 1, Serum, a neural tube defect (NTD) risk is not provided. For a stand-alone NTD-risk assessment, order MAFP / Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum. If the risk from the first trimester is below the established cutoff, an additional serum specimen is drawn in the second trimester for Sequential Maternal Screening, Part 2, Serum. Once that specimen is processed, information from both trimesters is combined and a report is issued. If results are positive, the patient is typically offered counseling and diagnostic testing (ie, amniocentesis). Alpha-Fetoprotein (AFP): AFP is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from a nonpregnancy level of 0.2 to about 250 ng/mL at 32-weeks gestation. If the fetus has an open neural tube defect (NTD), AFP is thought to leak directly into the amniotic fluid causing high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocoele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal-distress situations such as threatened abortion and fetal demise, also may show AFP elevations. Increased maternal serum AFP values also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower values have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18. Unconjugated Estriol (uE3): Estriol, the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the intact feto-placental unit. Estriol exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of uE3 in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates estriol to make it more water soluble for urinary excretion. Estriol levels increase during the course of pregnancy. Decreased uE3 has been shown to be a marker for Down syndrome and trisomy 18. Low levels of estriol also have been associated with overestimation of gestation, pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Human Chorionic Gonadotropin (hCG): hCG is a glycoprotein consisting of 2 noncovalently bound subunits. The alpha subunit is identical to the alpha subunits of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. The CGA gene (glycoprotein hormones, alpha polypeptide) is thought to have developed through gene duplication from the LH gene in a limited number of mammalian species. hCG only plays an important physiological role in primates (including humans), where it is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total beta hCG levels are associated with Down syndrome, while decreased levels may be seen in trisomy 18. Elevations of hCG also can be seen in multiple pregnancies, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetalis. Inhibin A: Inhibins are a family of heterodimeric glycoproteins that consist of disulfide-linked alpha and beta subunits, primarily secreted by ovarian granulosa cells and testicular Sertoli cells. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major
forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta-A or a beta-B chain, they are designated as inhibin A or inhibin B, respectively. Together with the related activins, which are homodimers or heterodimers of beta-A and beta-B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the fetoplacental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibin A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibin A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibin A levels are typically higher in Down syndrome pregnancies). However, despite their similar behavior, measuring maternal serum inhibin A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for Down syndrome.

**Useful For:** Prenatal screening for Down syndrome and trisomy 18 Prenatal screening for neural tube defects: (this is only applicable to Part 2 [second trimester] of the test) -Part 2 (second trimester):
alpha-fetoprotein

**Interpretation:** Maternal screens provide an estimation of risk, not a diagnosis. A negative result indicates that the estimated risk falls below the screen cutoff. A positive result indicates that the estimated risk exceeds the screen cutoff. Neural Tube Defect (NTD): Screen-negative results indicate that the alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the screen cutoff of 2.50 MoM (5.33 MoM for twins). A negative screen does not guarantee the absence of an NTD. Screen-positive results indicate that the calculated AFP MoM is > or =2.50 MoM (5.33 MoM for twins). Positive results may indicate an increased risk for an open NTD. The actual risk depends on the level of AFP and the individual’s pretest risk of having a child with an NTD based on variables including family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD, but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with open NTDs have AFP MoM values >2.5. Down Syndrome: Sequential Maternal Screening, Part 2. Serum results are negative when the calculated risk is below 1/270 (0.37%). Negative results mean that the risk is less than the established cutoff; they do not guarantee the absence of Down syndrome. Results are positive when the risk is greater than the established cutoff (> or =1/270 in Sequential Maternal Screening, Part 2, Serum). Positive results are not diagnostic. When both Sequential Maternal Screening Part 1 and Part 2 are performed with a screen cutoff of 1/270, the combination of maternal age, nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 90% with a false-positive rate of approximately 3% to 4%. In practice, both the detection rate and false-positive rate vary with maternal age. Trisomy 18: In Part 2, the screen cutoff for trisomy 18 is 1 in 100 (1%). Risks that are > or =1% are screen-positive; positive results are not diagnostic. Risks <1% are screen-negative; negative results do not guarantee the absence of trisomy 18. Use caution when revising positive results with earlier dating. Babies with trisomy 18 tend to be small, which can lead to underestimation of gestational age and an increased risk of missing a true-positive. When both Sequential Maternal Screening Part 1 and Part 2 of sequential screening are performed with a screen cutoff of 1/100, the combination of maternal age, PAPP-A, AFP, uE3, and hCG, has an overall detection rate of approximately 90% with a false-positive rate of approximately 0.1%. Follow-up: Verify that all information used in the risk calculation is correct (maternal date of birth, gestational dating, etc). If any information is erroneous, contact the laboratory for a revision. Screen-negative results typically do not warrant further evaluation. If the results are positive, the patient is typically offered counseling, ultrasound, diagnostic testing, and, possibly, a referral to genetics counseling or a high-risk clinic.

**Reference Values:**
An interpretive report will be provided. See Interpretation section for more details.


**Serotonin Receptor Genotype (HTR2A and HTR2C)**

**Clinical Information:** Treatment with specific antidepressant and antipsychotic medications is often guided empirically. Despite the wide array of drugs available for treatment, some patients do not initially respond to treatment, and others who respond early may eventually relapse or develop serious side effects. Antidepressant selection may be more effectively guided by genotyping polymorphic genes encoding several cytochrome P450 enzymes, the serotonin transporter, and the serotonin (5-hydroxytryptamine) receptors HTR2A and HTR2C. (1) Drugs that bind to the serotonin receptors have a wide range of effects including altering the activation of the receptors, rendering them more or less sensitive to drug concentration, or blocking the receptor. Variations (polymorphisms) in the genes that encode for the serotonin receptor have been associated with different types of drug responses including: - Allelic variation in the HTR2A gene has been reported to affect response to selective serotonin reuptake inhibitors (SSRI) and risk for adverse drug reactions. (2) Patients predicted to respond poorly to SSRIs due to polymorphic variants in the HTR2A/2C serotonin receptors may be considered for switching to non-SSRI antidepressants. Allelic variations in the HTR2A gene has been linked with response to the antipsychotic drugs clozapine and aripiprazole. (3) - Treatment with antipsychotics results in significant weight gain (2-3 kg/m²) in some patients. Weight gain has been positively correlated with a polymorphism in the promoter of HTR2C (-759C). (4) Allele nomenclature: Gene Nucleotide Change Amino Acid Change HTR2A -1438G>A Promoter polymorphism HTR2A 74C>A Thr25Asp HTR2A IVS2+54538A>G Non-coding HTR2A 1354C>T His452Tyr HTR2C -759C>T Promoter polymorphism

**Useful For:** Guiding treatment choice of a selective serotonin reuptake inhibitor (SSRI) or non-SSRI antidepressant Guiding treatment choice in individuals who have a drug-metabolizer phenotype discordant with CYP450 genotypes Identifying patients who may benefit from treatment with the antipsychotic drug clozapine and aripiprazole Identifying those patients at risk of excessive weight gain when receiving antipsychotic medications

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

respond to treatment, and others who respond early may eventually relapse or develop serious side effects. Antidepressant selection may be more effectively guided by genotyping polymorphic genes encoding several cytochrome P450 enzymes, the serotonin transporter, and the serotonin (5-hydroxytryptamine) receptors HTR2A and HTR2C.(1) Drugs that bind to the serotonin receptors have a wide range of effects including altering the activation of the receptors, rendering them more or less sensitive to drug concentration, or blocking the receptor. Variations (polymorphisms) in the genes that encode for the serotonin receptor have been associated with different types of drug responses including: - Allelic variation in the HTR2A gene has been reported to affect response to selective serotonin reuptake inhibitors (SSRI) and risk for adverse drug reactions.(2) Patients predicted to respond poorly to SSRIs due to polymorphic variants in the HTR2A/2C serotonin receptors may be considered for switching to non-SSRI antidepressants. Allelic variation in the HTR2A gene has been linked with response to the antipsychotic drugs clozapine and aripiprazole.(3) - Treatment with antipsychotics results in significant weight gain (2-3 kg/m²) in some patients. Weight gain has been positively correlated with a polymorphism in the promoter of HTR2C (-759C).(4) Allele nomenclature Gene Nucleotide Change Amino Acid Change HTR2A 1438G>A Promoter polymorphism HTR2A 74C>A Thr25Asp HTR2A IVS2+54538 A>G Non-coding HTR2A 1354C>T His452Tyr HTR2C -759C>T Promoter polymorphism

**Useful For:** Guiding treatment choice of a (selective serotonin reuptake inhibitor) SSRI or non-SSRI antidepressant Guiding treatment choice in individuals who have a drug-metabolizer phenotype discordant with CYP450 genotypes Identifying patients who may benefit from treatment with the antipsychotic drug clozapine and aripiprazole Identifying those patients at risk of excessive weight gain when receiving antipsychotic medications Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### Serotonin Release Assay (SRA), LMWH

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>LMWH SRA Result</td>
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<tr>
<td>LMWH Low Dose, 0.1 U/mL</td>
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<tr>
<td>LMWH Low Dose, 1.0 U/mL</td>
</tr>
<tr>
<td>LMWH High Dose, 50 U/mL</td>
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A sample is considered negative if there is: <20% release

### Serotonin Release Assay, Unfractionated Heparin

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<td>LMWH Low Dose, 0.1 U/mL</td>
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<td>LMWH Low Dose, 1.0 U/mL</td>
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<tr>
<td>LMWH High Dose, 50 U/mL</td>
</tr>
</tbody>
</table>

A sample is considered negative if there is: <20% release

---

*FSRA* 57819  
**Serotonin Release Assay (SRA), LMWH**

*FSRAU* 57820  
**Serotonin Release Assay, Unfractionated Heparin**
Serotonin Release Assay, Unfractionated Heparin

Reference Values:
An interpretive comment included with results.

Serotonin Transporter Genotype, Blood

Clinical Information: Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter. The serotonin transporter (5-HTT) modulates neurotransmission by facilitating removal of serotonin from the synapse of serotonergic neurons, resulting in serotonin reuptake into the presynaptic terminus. Other designations for 5-HTT are SLC6A4 (solute carrier family 6 [neurotransmitter transporter, serotonin], member 4), hSERT, OCD1, SERT, sodium-dependent serotonin transporter, and 5-HT transporter. Selective serotonin reuptake inhibitors (SSRIs) block the action of the serotonin transporter and are used to treat depression and other neuropsychiatric disorders. Examples of SSRIs are fluoxetine (Prozac), fluvoxamine (Luvox), escitalopram oxalate (Lexapro), sertraline (Zoloft), citalopram (Celexa), and paroxetine (Paxil, Paxil CR). The 5-HTT gene is located at 17q11.1-q12 and is composed of 14 exons spanning 31 kb. A 44-base pair promoter insertion/deletion polymorphism called LPR, or linked polymorphic region, produces alleles described as long or short. The short allele is dominant and results in decreased concentration of the transporter protein and a poorer response to stressful events. While individuals homozygous for the long allele (l/l) may demonstrate response to SSRI therapy in 3 to 4 weeks, individuals with the short allele (l/s or s/s) may respond more slowly to SSRI therapy and may benefit from a longer trial before considering switching to another antidepressant. Even 1 copy of the short allele (heterozygous) decreases the amount of the transporter protein present, increasing the time to response.

Useful For: Evaluating patients who have failed therapy with selective serotonin reuptake inhibitors (SSRIs) Evaluating patients with treatment-resistant depression Predicting response time to improvement with SSRIs Identifying patients who might respond favorably to a class of antidepressants other than SSRI Identifying patients who have diminished amounts of the serotonin transporter and, hence, an altered response to SSRI therapeutics

Interpretation: The normal (wildtype) allele yields a long product (l/l). The variant is short/short (s/s). Heterozygotes have a l/s genotype. Individuals homozygous for the long allele (l/l) may respond more rapidly to selective serotonin reuptake inhibitors (SSRI) therapy. Individuals homozygous for the short allele (s/s) may respond more slowly to SSRI therapy and may benefit from a longer trial before considering switching to another antidepressant. Even 1 copy of the short allele (heterozygous) decreases the amount of the transporter protein present, increasing the time to response.

Reference Values:
An interpretive report will be provided.


Serotonin Transporter Genotype, Saliva

Clinical Information: Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter. The serotonin
transporter (5-HTT) modulates neurotransmission by facilitating removal of serotonin from the synapse of serotonergic neurons, resulting in serotonin reuptake into the presynaptic terminus. Other designations for 5-HTT are SLC6A4 (solute carrier family 6 [neurotransmitter transporter, serotonin], member 4), hSERT, OCD1, SERT, sodium-dependent serotonin transporter, and 5-HT transporter. Selective serotonin reuptake inhibitors (SSRIs) block the action of the serotonin transporter and are used to treat depression and other neuropsychiatric disorders. Examples of SSRIs include fluoxetine (Prozac), fluvoxamine (Luvox), escitalopram oxalate (Lexapro), sertraline (Zoloft), citalopram (Celexa), and paroxetine (Paxil, Paxil CR). The 5-HTT gene is located at 17q11.1-q12 and is composed of 14 exons spanning 31 kb. A 44-base pair promoter insertion/deletion polymorphism called LPR, or linked polymorphic region, produces alleles described as long or short. The short allele is dominant and results in decreased concentration of the transporter protein and a poorer response to stressful events. While individuals homozygous for the long allele (l/l) may demonstrate response to SSRI therapy in 3 to 4 weeks, individuals with the short allele (l/s or s/s) may respond to SSRI therapy more slowly, taking up to 12 weeks.

**Useful For:** Qualifying participants for clinical trials Evaluating patients who have failed therapy with selective serotonin reuptake inhibitors (SSRIs) Evaluating patients with treatment-resistant depression Predicting response time to improvement with SSRIs Identifying patients who might respond favorably to nonselective antidepressants Identifying patients who have diminished amounts of the serotonin transporter and, hence, an altered response to SSRI therapeutics Genotyping patients who prefer not to have venipuncture done

**Interpretation:** The normal (wildtype) allele yields a long product (l/l). The variant is short/short (s/s). Heterozygotes have a l/s genotype. Individuals homozygous for the long allele (l/l) may respond more rapidly to selective serotonin reuptake inhibitor (SSRI) therapy. Individuals homozygous for the short allele (s/s) may respond more slowly to SSRI therapy and may benefit from a longer trial before considering switching to another antidepressant. Even 1 copy of the short allele (heterozygous) decreases the amount of the transporter protein present, increasing the time to response.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly serotonin, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by serotonin. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of serotonin. Because midgut tumors drain into the portal circulation, which passes into the liver, undergoing extensive hepatic (first-pass) serotonin degradation, symptoms do not usually occur until liver or other distant metastases have developed, producing serotonin that bypasses the hepatic degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urine serotonin, urine 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells. Urine serotonin is, in most circumstances, the least likely marker to be elevated (see Interpretation).

**Useful For:** The diagnosis of a small subgroup of carcinoid tumors that produce predominately 5-hydroxytryptophan (5-HTP), but very little serotonin and chromogranin A Follow-up of patients with known or treated carcinoid tumors that produce predominately 5-HTP, but very little serotonin and chromogranin A

**Interpretation:** It is usually impossible to diagnose asymptomatic, small carcinoid tumors by measurement of serum or urine serotonin, urine 5 hydroxyindoleacetic acid (5-HIAA), or serum chromogranin A. By contrast, 1 or more of these markers are elevated in most patients with more advanced and symptomatic tumors, usually to levels several times the upper limit of the reference interval. In patients with advanced and symptomatic tumors the following patterns of tumor marker elevations are observed: - Serum or whole blood serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors, because foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little, if any, serotonin. - Urine 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. - Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. - Urine serotonin is in most circumstances the least likely marker to be elevated. The exception is tumors (usually foregut tumors) that produce predominately 5-HTP, rather than serotonin, and also secrete little, if any, chromogranin A. In this case, circulating chromogranin A, circulating serotonin levels, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels. Urine serotonin measurements are not commonly employed in carcinoid tumor follow-up. The exceptions are patients with tumors that almost exclusively secrete 5-HTP, as summarized above. In these individuals, urine serotonin is the tumor marker of choice to monitor disease progression. In all other patients, disease progression is monitored best using urinary 5-HIAA and serum chromogranin A measurements. These markers are usually proportional to the patient's tumor burden over a wide range of tumor extent and tumor secretory activity.

**Reference Values:**
< or =210 mcg/24 hours
Reference values apply to all ages.

**Clinical References:**

**Serotonin, Blood**

**Clinical Information:** Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content. Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver, 30% to 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular, tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

**Useful For:** In conjunction with, or as an alternative to, 5-hydroxyindoleacetic acid (5-HIAA) or serum chromogranin A measurements as a first-line test in the diagnosis of carcinoid syndrome, including the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing As a second-line test (5-HIAA and serum chromogranin A measurement are first-line tests) in the follow-up of patients with known or treated carcinoid tumors

**Interpretation:** Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations >1,000 ng/mL. However, elevations >400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A
measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HTP, rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to 5-HT, leading to high urinary 5-HT levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

Reference Values:
< or =330 ng/mL


Serotonin, Serum

Clinical Information: Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HTP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content. Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver 30% - 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejenum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of
carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

**Useful For:** In conjunction with, or as an alternative to, with 5 hydroxyindoleacetic acid (5-HIAA) or serum chromogranin A measurements as a first-line test in the diagnosis of carcinoid syndrome. This includes the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing. As a second-line test (5-HIAA or serum chromogranin A measurements are first-line tests) in the follow-up of patients with known or treated carcinoid tumors.

**Interpretation:** Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations >1,000 ng/mL. However, elevations >400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5 hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and therefore may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HTP, rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to 5-HT, leading to high urinary 5-HT levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

**Reference Values:**
< or =230 ng/mL

**Clinical References:**

**FSERT 91345**

**Sertraline (Zoloft) and Desmethylsertraline**

**Reference Values:**

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<thead>
<tr>
<th>Component</th>
<th>Reference Range</th>
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<tbody>
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<td>Sertraline</td>
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<tr>
<td>Desmethylsertraline</td>
<td>ng/mL</td>
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</table>

No reference range provided
The stated reference range is the range of observed steady-state concentrations in individuals receiving therapeutic dosage regimens of sertraline. This is not a defined therapeutic range.

**FSESG**

**Sesame Seed IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**SESA**

**Sesame Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
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</tr>
<tr>
<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.

### Sex Chromosome Determination, FISH, Tissue

**Clinical Information:** Genotypically normal females possess 2 X chromosomes (XX); genotypically normal males possess 1 X chromosome and 1 Y chromosome (XY). Determining the sex chromosome complement in a tissue specimen can be used to: -Identify opposite sex-donor cells post-transplant -Help resolve cases of suspected sample mix-up

**Useful For:** Identifying the sex chromosome complement in paraffin-embedded tissues

**Interpretation:** An interpretive report is provided.

**Reference Values:** An interpretive report will be provided.


### Sex Hormone-Binding Globulin (SHBG), Serum

**Clinical Information:** Sex hormone-binding globulin (SHBG), a homodimeric 90,000 to 100,000 molecular weight glycoprotein, is synthesized in the liver. Metabolic clearance of SHBG is biphasic, with a fast initial distribution from vascular compartment into extracellular space (half-life of a few hours), followed by a slower degradation phase (half-life of several days). SHBG binds sex steroids with high affinity (KD approximately 10(-10)M), dihydrotestosterone (DHT) ->testosterone (T) ->estrone/estradiol (E). Although each monomeric subunit contains 1 steroid binding site, the dimer tends to bind only a single sex-steroid molecule. The main function of SHBG is sex-steroid transport within the blood stream and to extravascular target tissues. SHBG also plays a key role in regulating bioavailable sex-steroid concentrations through competition of sex steroids for available binding sites and fluctuations in SHBG concentrations. Because of the higher affinity of SHBG for DHT and T, compared to E, SHBG also has profound effects on the balance between bioavailable androgens and estrogens. Increased SHBG levels may be associated with symptoms and signs of hypogonadism in men, while decreased levels can result in androgenization in women. SHBG levels in prepubertal children are higher than in adults. With the increase in fat mass during early puberty they begin to fall, a process that accelerates as androgen levels rise. Men have lower levels compared with women and nutritional status is inversely correlated with SHBG levels throughout life, possibly mediated by insulin resistance. Insulin resistance, even without obesity, results in lower SHBG levels. This is associated with increased intra-abdominal fat deposition and an unfavorable cardiovascular risk profile. In postmenopausal women, it may also predict the future development of type 2 diabetes mellitus. Androgens and norethisterone-related synthetic progestin also decrease SHBG in women. Endogenous or exogenous thyroid hormones or estrogens increase SHBG levels. In men, there is also an age-related gradual rise, possibly secondary to the mild age-related fall in testosterone production. This process can result in bioavailable testosterone levels that are much lower than would be expected based on total testosterone measurements alone.

**Useful For:** Diagnosis and follow-up of women with symptoms or signs of androgen excess (eg, polycystic ovarian syndrome and idiopathic hirsutism) An adjunct in monitoring sex-steroid and anti-androgen therapy An adjunct in the diagnosis of disorders of puberty An adjunct in the diagnosis and
follow-up of anorexia nervosa An adjunct in the diagnosis of thyrotoxicosis (tissue marker of thyroid hormone excess) A possible adjunct in diagnosis and follow-up of insulin resistance and cardiovascular and type 2 diabetes risk assessment, particularly in women In laboratories without access to bioavailable testosterone or equilibrium dialysis-based “true” free testosterone assays, sex hormone-binding globulin measurement is crucial in cases when assessment of the free testosterone fraction (aka free androgen index or calculated free testosterone) is required. At Mayo Medical Laboratories, both bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) and free testosterone (TGRP / Testosterone, Total and Free, Serum) measurements are available. Free testosterone (TGRP) is measured by equilibrium dialysis, obviating the need for sex hormone-binding globulin measurements to calculate free androgen fractions.

Interpretation: Many conditions of mild-to-moderate androgen excess in women, particularly polycystic ovarian syndrome, are associated with low sex hormone-binding globulin (SHBG) levels. Most of these women are also insulin resistant and many are obese. A defect in SHBG production could lead to bioavailable androgen excess, in turn causing insulin resistance that depresses SHBG levels further. There are rare cases of SHBG mutations that clearly follow this pattern. SHBG levels are typically very low in these individuals. However, in most patients, SHBG levels are mildly depressed or even within the lower part of the normal range. In these patients, the primary problem may be androgen overproduction, insulin resistance, or both. A definitive cause cannot be usually established. Any therapy that either increases SHBG levels (eg, estrogens or weight loss), reduces bioactivity of androgens (eg, androgen receptor antagonists, alpha-reductase inhibitors), or reduces insulin resistance (eg, weight loss, metformin, peroxisome proliferator-activated receptor [PPAR] gamma agonists), can be effective. Improvement is usually associated with a rise in SHBG levels, but bioavailable or free testosterone levels should also be monitored. The primary method of monitoring sex-steroid or antiandrogen therapy is direct measurement of the relevant sex-steroids and gonadotropins. However, for many synthetic androgens and estrogens (eg, ethinyl-estradiol) clinical assays are not available. In those instances, rises in SHBG levels indicate successful anti-androgen or estrogen therapy, while falls indicate successful androgen treatment. Adult SHBG levels in boys with signs of precocious puberty support that the condition is testosterone driven, rather than representing premature adrenarche. Patients with anorexia nervosa have high SHBG levels. With successful treatment, levels start to fall as nutritional status improves. Normalization of SHBG precedes, and may be predictive of, future normalization of reproductive function. Thyrotoxicosis increases SHBG levels. In situations when assessment of true functional thyroid status may be difficult (eg, patients receiving amiodarone treatment, individuals with thyroid hormone transport-protein abnormalities, patients with suspected thyroid hormone resistance or suspected inappropriate thyroid-stimulating hormone [TSH] secretion such as a TSH-secreting pituitary adenoma), an elevated SHBG level suggests tissue thyrotoxicosis, while a normal level indicates euthyroidism or near-euthyroidism. In patients with gradual worsening of thyrotoxicosis (eg, toxic nodular goiter), serial SHBG measurement, in addition to clinical assessment, thyroid hormone, and TSH measurement, may assist in the timing of treatment decisions. Similarly, SHBG measurement may be of value in fine-tuning suppressive TSH therapy for patients with nodular thyroid disease or treated thyroid cancer. Results are not definitive in the short-term in patients receiving drugs that displace total thyroxine (T4) from albumin. SHBG is also produced by placental tissue and therefore values will be elevated during pregnancy. Reference ranges for pregnant females have not been established in our institution. In patients with known insulin resistance, "metabolic syndrome," or high risk of type 2 diabetes (eg, women with a history of gestational diabetes), low SHBG levels may predict progressive insulin resistance, cardiovascular complications, and progression to type 2 diabetes. An increase in SHBG levels may indicate successful therapeutic intervention. A genetic variant of SHBG (Asp327->Asn) introduces an additional glycosylation site in 10% to 20% of the population, resulting in significantly slower degradation. These individuals tend to have higher SHBG levels for any given level of other factors influencing SHBG.

Reference Values:

<table>
<thead>
<tr>
<th>Tanner Stages*</th>
<th>Mean Age</th>
<th>Reference Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>7.1</td>
<td>31-167</td>
</tr>
<tr>
<td>Stage II</td>
<td>11.5</td>
<td>49-179</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6</td>
<td>5.8-182</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1</td>
<td>14-98</td>
</tr>
</tbody>
</table>
Stage V	18.0

10-57 *Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Females

Tanner Stages* | Mean Age | Reference Range (nmol/L)
---|---|---
Stage I	7.1	43-197
Stage II	10.5	7.7-119
Stage III	11.6	31-191
Stage IV	12.3	31-166
Stage V	14.5	18-144

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

**ADULTS**
Males: 10-57 nmol/L
Females (non-pregnant): 18-144 nmol/L

**Clinical References:**

**SRYF 35301**

**Sex-Determining Region Y, Yp11.3 Deletion, FISH**

**Clinical Information:** This test is appropriate for individuals with a 46,XX karyotype and phenotypically normal male external genitalia, a 46,XY karyotype and phenotypically normal female external genitalia, clinical features suggestive of 46,XX testicular disorder of sex development with normal male external genitalia, and clinical features suggestive of 46,XY complete gonadal dysgenesis. The SRY (sex-determining region on the Y chromosome) gene is required for normal embryonic wolffian (male) genital development, although numerous other genes are involved in completing the process of normal male development. Some gene mutations block the action of SRY in development. Thus, a 46,XY individual with an SRY deletion or mutation will develop as a female, and a 46,XX individual with translocation of SRY to 1 X chromosome will develop as a male. Structural abnormalities of the Y chromosome result in a spectrum of abnormalities from primary infertility (male or female) to various forms of ambiguous genitalia. SRY-negative 46,XX males often have ambiguous genitalia, whereas those who are positive for SRY usually have a normal male phenotype with azoospermia. SRY-negative 46,XY females may have another mutation, such as 1 involving the SOX9 gene. We recommend conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood) to detect Y chromosome abnormalities and to rule out other chromosome abnormalities or translocations, and FISH studies to detect cryptic translocations involving the SRY region that are not demonstrated by

Current as of July 8, 2016 11:28 am CDT
conventional chromosome studies.

**Useful For:** Detecting the deletion or addition of the SRY gene in conjunction with conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood)

**Interpretation:** Any male individual with an SRY signal on a structurally normal Y chromosome is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe. Any patient with a FISH signal on an X chromosome will be reported as having a cryptic X;Y translocation involving the critical region.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Sheep Wool, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Shiga Toxin, Molecular Detection, PCR, Feces

Clinical Information: Shiga toxins (also known as Shiga-like toxins, Vero toxins, or Vero-like toxins) are encoded by some strains of Escherichia coli, most notably O157:H7. Shiga toxin can also be produced by other serogroups of enterohemorrhagic Escherichia coli (EHEC), as well as Shigella dysenteriae type 1. Generally, Shiga toxin-producing organisms cause bloody diarrhea, although this is not universal. Unlike some bacterial gastrointestinal infections, antimicrobial therapy is contraindicated, as antimicrobials may exacerbate disease. Treatment is primarily supportive (eg, hydration). A complication of infection by an organism producing Shiga toxin is hemolytic uremic syndrome (HUS). The percentage of people that develop HUS varies among outbreaks of Escherichia coli O157:H7, but generally ranges from 3% to 20%. HUS is characterized by a triad of findings: hemolytic anemia, thrombocytopenia, and kidney failure. Most people recover completely, however, some require permanent dialysis, and some die as a result of complications. Several diagnostic methods available for the detection of EHEC lack sensitivity, are labor intensive, or have a long turnaround time. There are more than 160 serogroups of EHEC; the first serogroup to be associated with HUS was O157:H7. This is also the serogroup that is most commonly implicated in outbreaks. EHEC O157:H7 is detectable as nonfermenting colonies when cultured on sorbitol MacConkey (SMAC) agar, but the majority of non-O157:H7 Shiga toxin-producing Escherichia coli strains ferment sorbitol and, therefore, are undetectable by this method. The Vero cell line is susceptible to the Shiga toxin, but the assay can take up to 48 hours and is nonspecific. Commercial enzyme-linked immunosorbent assay (ELISA) antigen detection kits have a sensitivity of 90% when compared to culture, but an overnight enrichment step is necessary for adequate sensitivity. PCR detection of stx, the gene encoding Shiga toxin, directly from stool specimens is a sensitive and specific technique, providing same-day results. PCR assay identifies non-O157:H7 Shiga toxin-producing bacteria, extending the utility beyond strains identifiable on SMAC agar.

Useful For: Sensitive, specific, and rapid detection of the presence of Shiga toxin-producing organisms such as Escherichia coli O157:H7 and Shigella dysenteriae type 1 in stool

Interpretation: A positive PCR result indicates the likely presence of Shiga toxin-producing Escherichia coli in the specimen. Although Shigella dysenteriae serotype 1 may produce a positive result, it is extremely rare in the United States. A negative result indicates the absence of detectable Shiga toxin DNA in the specimen, but does not rule out the presence of Shiga toxin-producing Escherichia coli, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of the Shiga toxin gene in quantities less than the limit of detection of the assay. Shiga toxins are encoded on mobile genetic elements and can theoretically be lost by their bacterial host.

Reference Values:
Not applicable

Short Ragweed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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| 6     | > or =100| Strongly positive Reference values apply to all ages.


Short-Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency, Full Gene Analysis

Clinical Information: Short-chain acyl-CoA dehydrogenase (SCAD) catalyzes the first step in the mitochondrial beta-oxidation of fatty acids with a chain length of 6 to 4 carbons. SCAD deficiency is a rare autosomal recessive condition. The clinical phenotype of SCAD shows considerable variability and is incompletely defined. Of those reported cases, hypoglycemia, developmental delay, and muscle hypotonia are the most common indicated features. The diagnosis of SCAD deficiency is challenging and should be based on the clinical presentation, 2 or more findings of ethylmalonic aciduria, and determination of fatty acid flux in fibroblasts indicating deficient SCAD activity. Molecular genetic analysis of the gene associated with SCAD (ACADS) may confirm the biochemical phenotype of SCAD deficiency. The first step in evaluation for SCAD deficiency is identification of 2 or more findings of ethylmalonic aciduria, as
Ethylmalonic aciduria is a common, although not specific, laboratory finding in patients with SCAD deficiency. Determination of fatty acid flux in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) is warranted for an individual with 2 or more findings of ethylmalonic aciduria. DNA sequencing of the ACADS gene is typically utilized only when SCAD deficiency is identified through biochemical analysis. The ACADS gene, associated with SCAD deficiency, is located on chromosome 12q22 and consists of 10 exons. Molecular genetic studies revealed that some patients carry ACADS gene mutations that cause complete absence of SCAD activity, while others carry ACADS gene variants (511C->T;625G->A) that may confer disease susceptibility only in association with other factors. The allele frequencies in the general population of the 511C->T and 625G->A gene variants are 3% and 22%, respectively. The presence of 2 of these gene variants is not considered an independent diagnostic marker for SCAD deficiency. Although further investigation is needed, it is most likely that these variants are not clinically significant. Identification of 2 ACADS gene mutations that cause complete absence of SCAD activity alone is not sufficient to explain or determine possible clinical phenotype or prognosis. The clinical significance of carrying 2 mutations is often uncertain. Therefore, the results of ACADS gene sequencing for SCAD deficiency should be interpreted in light of the clinical presentation and biochemical findings in each case.

**Useful For:** Preferred molecular analysis to confirm a diagnosis of short-chain acyl-CoA dehydrogenase deficiency (as a follow-up to the biochemical analyses only)

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FSHOX 57127**

**SHOX-DNA-DxTM**

**Reference Values:**
Testing is complete. Report has been attached in MayoAccess.

**FSHRG 57542**

**Shrimp IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Shrimp, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Silicon, Serum/Plasma

Reference Values:

Reporting limit determined each analysis.

Generally: Less than 0.05 mg/dL.
Silicon concentrations are influenced by diet, especially vegetable intake.

Silk, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Silver Birch, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Silver, Serum**

**Clinical Information:** The bacteriostatic properties of silver have long been recognized. In the 19th century, silver nitrate was used to treat gonorrheal ophthalmia in the newborn. Current medical uses of silver-containing compounds include sulfadiazine ointment for burn patients and some nasal decongestants. Silver-coated sutures and catheters have shown some effectiveness against a broad range of bacteria. Colloidal silver is contained in various over-the-counter preparations sold in health food stores. Environmental silver exposure can be the result of manufacture of silver nitrates as germicides, antiseptics, caustics, and analytical reagents; and for use in photography, mirrors, plating, inks, dyes, and porcelain. Additionally, sources of exposure include manufacture of silver salts as catalysts in oxidation-reduction and polymerization reactions; in chemical synthesis, in glass manufacture, in silver plating, as laboratory reagents, and in medicinal compounds. Silver is not an essential constituent of the human body. Silver metabolism in humans has been inadequately studied and little reliable data is available. Some individuals seem to absorb silver selectively. Silver deposits in many organs, including the subepithelium of skin and mucous membranes producing a syndrome called argyria (greying of the skin). Argyria is associated with growth retardation, hemopoiesis, cardiac enlargement, degeneration of the liver, and destruction of renal tubules.

**Useful For:** Determination of silver exposure

**Interpretation:** A finding of silver >1,000 ng/mL is indicative of acute silver exposure. Argyria occurs when silver levels are >2,000 ng/mL. No link between moderately elevated silver serum levels and symptoms has been reported in peer-reviewed medical literature.

**Reference Values:**

<15 ng/mL

Sinemet, Serum/Plasma

Reference Values:
Reporting limit determined each analysis.

Levodopa
Synonym(s): Sinemet Constituent

Carbidopa
Synonym(s): Sinemet Constituent

Following a single oral dose of 100 mg Levodopa and 25 mg Carbidopa (conventional Sinemet tablet):
Approximately 0.3 mcg Levodopa/mL and 0.05 mcg Carbidopa/mL plasma at 1 hour post dose. Average
steady-state trough plasma levels in elderly patients following a regimen of Sinemet CR (50 mg
Carbidopa and 200 mg Levodopa sustained release tablets) three times daily:
  0.16 mcg Levodopa/mL
  0.07 mcg Carbidopa/mL

Sirolimus, Blood

Clinical Information: Sirolimus is a macrolide antibiotic, isolated from Streptomyces hygroscopicus,
with potent effects including suppression of T- and B-cell proliferation and antineoplastic and antifungal
activity. It inhibits the protein kinase mTOR to arrest the cell cycle; it has no effects on calcineurin and,
therefore, can be used in addition to cyclosporine or tacrolimus, or as a substitute in patients intolerant to
these drugs. Sirolimus is metabolized by CYP3A4, thus, blood concentrations are affected by drugs that
inhibit or induce this enzyme. The pharmacokinetic interaction between sirolimus and cyclosporine or
tacrolimus increases both therapeutic immunosuppression and the toxicity of these agents; lower doses are
required with combined use. Adverse effects of sirolimus are generally concentration dependent, making
therapeutic drug monitoring essential. Trough sirolimus concentrations are generally measured every 5
days. Target concentrations vary depending on concomitant therapy, time post transplant, the desired
degree of immunosuppression, and adverse effects. When given with cyclosporine or tacrolimus, the
therapeutic range for sirolimus is generally between 4 and 12 ng/mL with minimal added benefit for
concentrations >10 ng/mL. When sirolimus is given without calcineurin inhibitors, higher trough levels
are needed; usually 12 to 20 ng/mL, but occasionally up to 20 to 30 ng/mL.

Useful For:
Monitoring whole blood sirolimus concentration during therapy, particularly in individuals
coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize
immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to sirolimus with trough whole blood levels
4 to 20 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications.
Therapeutic ranges are based on specimens drawn at trough (ie, immediately before a scheduled dose).
Blood drawn at other times will yield higher results. The assay is specific for sirolimus; it does not
cross-react with cyclosporine, cyclosporine metabolites, tacrolimus, tacrolimus metabolites, or sirolimus
metabolites. Results by liquid chromatography with detection by liquid chromatography-tandem mass
spectrometry are approximately 30% less than by immunoassay.

Reference Values:
4-20 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant
immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be
interpreted in conjunction with this clinical information and any physical signs/symptoms of
rejection/toxicity.

Clinical References: 1. Kahan BD: Ten years of mTOR inhibitor therapy. Transplant Proc

**SLIRV**

35549

**Slide Review in Molecular Genetics (Bill Only)**

**Reference Values:**
This test is for billing purposes only. This is not an orderable test.

**SM**

81358

**Sm Antibodies, IgG, Serum**

**Clinical Information:** Sm is a small nuclear ribonucleoprotein composed of several protein autoantigens designated B, B1, D, E, F, and G, which range in size from 11 kD to 26 kD. Sm antibodies are specific for lupus erythematosus (LE) and occur in approximately 30% of LE patients. The levels of Sm antibodies remain relatively constant over time in patients with LE and are usually found in patients that also have RNP antibodies.(1,2) Sm is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENAs). The other ENAs are RNP, SS-A/Ro, and SS-B/La. Each ENA is composed of 1 or more proteins associated with small nuclear RNA species (snRNP) ranging in size from 80 to approximately 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren's syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive result for anti-Sm antibodies is consistent with a diagnosis of lupus erythematosus.

**Reference Values:**
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


**SMADZ**

35551

**SMAD4 Gene, Full Gene Analysis**

**Clinical Information:** Juvenile polyposis syndrome (JPS) is a rare hereditary cancer predisposition syndrome caused by mutations in the SMAD4 or BMPR1A genes. JPS is characterized by the presence of multiple histologically defined juvenile polyps in the upper and/or lower gastrointestinal (GI) tract and an increased risk for GI cancers. Age of onset for cancer development is typically in the second or third decade of life, although some patients present with a more severe infantile-onset form of the disease. JPS is inherited in an autosomal dominant fashion, although a significant proportion of probands have no family history. Approximately 50% of patients with JPS have an identifiable mutation in the SMAD4 or BMPR1A genes. Of note, some patients with mutations in the SMAD4 gene exhibit a combined juvenile polyposis/hereditary hemorrhagic telangiectasia phenotype (JP/HHT). Clinical features of HHT include development of arteriovenous malformations (AVMs) of the skin, mucosa, and viscera; spontaneous,
recurrent epistaxis (nosebleeds); as well as additional complications such as transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage.

**Useful For:** Confirmation of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia for patients with clinical features. This test should be ordered only for individuals with symptoms suggestive of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia. Asymptomatic patients with a family history of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia should not be tested until a mutation has been identified in an affected family member.

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

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**Small Lymphocytic Lymphoma, FISH, Tissue**

**Clinical Information:** Small lymphocytic lymphoma (SLL) is the nonleukemic form of chronic lymphocytic leukemia (CLL), the most common adult leukemia in North America. The most common cytogenetic abnormalities detected in CLL are deletions of 6q, 11q, 13q, and 17p, trisomy 12, and the occasional occurrence of IGH translocations at 14q32. Cytogenetics has proven to be a reliable predictor of outcome for patients with CLL. It is unknown if SLL has the same prognostic significance when these genetic abnormalities are observed. This FISH test detects an abnormal clone in approximately 65% of patients with SLL. Patients with t(11;14)(q13;q32) associated with CCND1/IGH fusion, have mantle cell lymphoma which can be distinguished from SLL and other B-cell lymphomas with this assay. Patients with t(14;18)(q32;q21) or t(14;19)(q32;q13.3) may have an atypical form of SLL or another low-grade B-cell lymphoma.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with small lymphocytic lymphoma (SLL) and other low-grade B-cell lymphomas. Distinguishing patients with 11;14 translocations who have mantle cell lymphoma from patients who have SLL.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. A positive result is not diagnostic for small lymphocytic lymphoma, but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
1. World Health Organization Classification of Tumours. Pathology and
Smith-Lemli-Opitz Screen, Plasma

**Clinical Information:** Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play important roles in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive.

Smith-Lemli-Opitz syndrome (SLO) is an autosomal recessive disorder caused by mutations in the DHCR7 gene leading to a deficiency of the 7-dehydrocholesterol reductase enzyme. It is characterized biochemically by markedly increased plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) levels. Clinically, features can include microcephaly, growth retardation, developmental delay, dysmorphic facial features, cleft palate, limb abnormalities (especially 2-3 syndactyly of the toes and postaxial polydactyly), and heart and kidney malformations. However, the clinical spectrum ranges from mild to severe with some mildly affected individuals presenting with only 2 to 3 toe syndactyly and mild cognitive impairment. The reported incidence is between 1 in 10,000 and 1 in 60,000, but it may be more prevalent due to underdiagnosis of mildly affected individuals. Other disorders of cholesterol biosynthesis, including desmosterolosis (desmosterol reductase deficiency) and sitosterolemia, may present with similar manifestations. These disorders can be detected biochemically by performing a quantitative profile of plasma sterols (STER / Sterols, Plasma).

**Useful For:** Diagnosis of Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)

**Interpretation:** Elevated plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) are highly suggestive of a biochemical diagnosis of Smith-Lemli-Opitz (SLO). Mild elevations of these cholesterol precursors can be detected in patients with hypercholesterolemia and patients treated with haloperidol. However, the 7-DHC to cholesterol ratio is only elevated in SLO patients.

**Reference Values:**
- Negative (reported as positive or negative)
- Quantitative results are provided when positive.

**Clinical References:**
Deletion/Duplication, FISH

**Clinical Information:** This test is appropriate for individuals with clinical features suggestive of Smith-Magenis syndrome and Potocki-Lupski syndrome. Smith-Magenis syndrome is associated with a deletion of the proximal short arm of chromosome 17, including the critical RAI1 gene region. Although the phenotype is variable, the syndrome can be suspected in patients with failure to thrive, brachycephaly (short head), prominent forehead, microcephaly (small head), flat and broad midface, strabismus, myopia, malformed ears, high and cleft palate, prognathism (protruding mandible), short and broad hands and feet, scoliosis (laterally curved spine), and cryptorchidism (undescended testes). Unusual features of the syndrome include specific self-destructive behavior, including insertion of foreign objects into bodily orifices, pulling out fingernails and toenails, and sleep abnormalities (especially disturbed rapid eye movement sleep). Mental retardation is variable but usually severe with seizures and hyperactivity. Patients with duplications of this region (Potocki-Lupski syndrome) tend to have a milder but overlapping phenotype. FISH studies are highly specific and do not exclude other chromosome abnormalities. For this reason, we recommend that patients suspected of having Smith-Magenis or Potocki-Lupski syndromes also have conventional chromosome studies (CMS / Chromosome Analysis, Blood) performed to rule out other chromosome abnormalities or translocations.

**Useful For:** Establishing a diagnosis of Smith-Magenis syndrome Establishing a diagnosis of Potocki-Lupski syndrome Detecting cryptic rearrangements involving 17p11.2, that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern (2 signals for RAI1) in each metaphase is considered negative for a deletion or duplication in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the RAI1 critical region will be reported as having a deletion of the regions tested by this probe. This is consistent with a diagnosis of 17p11.2 deletion (Smith-Magenis) syndrome. Any patient with a FISH signal pattern indicating additional critical region signals will be reported as having a duplication of the regions tested by this probe. This is consistent with a diagnosis of 17p11.2 duplication (Potocki-Lupski) syndrome.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Smooth Muscle Antibodies, Serum

**Clinical Information:** Sera from patients with autoimmune chronic active hepatitis contain antibodies to smooth muscle antigens that are detectable by indirect immunofluorescence on substrates that contain smooth muscle. The antibodies are predominantly of the IgG isotype. Other diseases in this differential diagnosis group include primary biliary cirrhosis, chronic viral hepatitis, and alcoholic chronic hepatitis.

**Useful For:** Evaluating patients with chronic liver disease in whom the diagnosis of chronic active autoimmune hepatitis is suspected

**Interpretation:** Antibody titers in the range of 80 to 320 occur commonly in patients with active chronic hepatitis; lower titers (usually <80) may occur in the other conditions mentioned earlier.

**Reference Values:**
Negative
If positive, results are titered.
Reference values apply to all ages.
**Clinical References:** Czaia AJ, Homburger HA: Autoantibodies in liver disease. Gastroenterology 2001;120:239-249

**SFBER 57962**

**Smut Bermuda (Ustilago cynodontis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FCRNS 57961**

**Smut Corn (Ustilago maydis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FSJON 57963**

**Smut Johnson (Sphacelotheca cruenta) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FWHTS 57965**

**Smut Wheat (Ustilago tritici) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**SNAIL 82344**

**Snail, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
<td></td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Sodium, 24 Hour, Urine**

**Clinical Information:** Sodium (Na+) is the primary extracellular cation. Sodium is responsible for almost one half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl) which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/d, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Sodium is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

**Useful For:** Assessing acid-base balance, water balance, water intoxication, and dehydration

**Interpretation:** Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night being only 20% of the peak rate during the day. Sodium may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values <10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to non-renal causes.

**Reference Values:**

41-227 mmol/24 hours

**NABF** 8039

**Sodium, Body Fluid**

**Reference Values:**
Not applicable

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by Burtis and Ashwood. Philadelphia, WB Saunders Co, 1994

**RNAUR** 84522

**Sodium, Random, Urine**

**Clinical Information:** Sodium (Na+) is the primary extracellular cation. Na+ is responsible for almost one half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl), which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/d, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Na+ is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

**Useful For:** Assessing acid-base balance, water balance, water intoxication, and dehydration

**Interpretation:** Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night being only 20% of the peak rate during the day. Na+ may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values <10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to nonrenal causes.

**Reference Values:**
No established reference values


**NACCL** 81692

**Sodium, Serum**

**Clinical Information:** Sodium is the primary extracellular cation. Sodium is responsible for almost one half the osmolality of the plasma and therefore plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of sodium in the body is a reflection of the balance between sodium intake and output. Hyponatremia (low sodium) is a predictable consequence of decreased intake of sodium, particularly that precipitated or complicated by unusual losses of sodium from the gastrointestinal tract (eg, vomiting and diarrhea), kidneys or sweat glands. Renal loss may be caused by inappropriate choice, dose or use of diuretics; by primary or secondary deficiency of aldosterone and other mineralocorticoids; or by severe polyuria. It is common in metabolic acidosis. Hyponatremia also occurs in nephrotic syndrome, hypoproteinemia, primary and secondary adrenocortical insufficiency and congestive heart failure. Symptoms of hyponatremia are a result of brain swelling and range from weakness to seizures, coma and death.
Hypernatremia (high sodium) is often attributable to excessive loss of sodium-poor body fluids. Hypernatremia is often associated with hypercalcemia and hypokalemia and is seen in liver disease, cardiac failure, pregnancy, burns, and osmotic diuresis. Other causes include decreased production of ADH or decreased tubular sensitivity to the hormone (i.e., diabetes insipidus), inappropriate forms of parenteral therapy with saline solutions, or high salt intake without corresponding intake of water. Hypernatremia occurs in dehydration, increased renal sodium conservation in hyperaldosteronism, Cushing’s syndrome, and diabetic acidosis. Severe hypernatremia may be associated with volume contraction, lactic acidosis and increased hematocrit. Symptoms of hypernatremia range from thirst to confusion, irritability, seizures, coma and death.

**Useful For:** Sodium assays are important in assessing acid-base balance, water balance, water intoxication, and dehydration.

**Interpretation:** Symptoms of hyponatremia depend primarily upon the rate of change in sodium concentration, rather than the absolute level. Typically, sodium values <120 mEq/L result in weakness; values <100 mEq/L in bulbar or pseudobulbar palsy; and values between 90 and 105 mEq/L in severe signs and symptoms of neurological impairment. Symptoms associated with hypernatremia depend upon the degree of hyperosmolality present.

**Reference Values:**
> or =12 months: 135-145 mmol/L
Reference values have not been established for patients that are less than 12 months of age.

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company. Philadelphia, PA, 1994

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**SOLEF 86310**

**Sole, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
</tbody>
</table>

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### Clinical References:

### CAPN 35594
**Solid Tumor Targeted Cancer Gene Panel by Next Generation Sequencing**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the United States Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. CAPN / Solid Tumor Targeted Cancer Gene Panel by Next Generation Sequencing is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in 50 genes known to be associated with cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with solid tumors. These data can also be used to help determine clinical trial eligibility for patients with mutations in genes not amenable to current FDA-approved targeted therapies. See Targeted Gene Regions Interrogated by Solid Tumor Targeted Cancer Gene Panel by Next Generation Sequencing in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying solid tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously Identifying specific mutations within genes known to be associated with response or resistance to specific cancer therapies Identifying mutations that may help determine prognosis for patients with solid tumors Assisting in establishing a diagnosis (eg, KIT and PDGFRA alterations for gastrointestinal stromal tumors)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


### FSFM 58015
**Soluble Fibrin Monomer**

**Reference Values:**
Negative

### FSLAA 57735
**Soluble Liver Antigen (SLA) Autoantibody**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Antibodies to soluble liver antigen (SLA) appear to be directed against the UGA-suppressor tRNA associated protein. These antibodies are highly specific for autoimmune hepatitis (AIH) and may rarely, be the only autoantibodies detected in serum from such patients. Antibodies to SLA are most closely associated with AIH type 1; the presence of these antibodies in patients with cryptogenic hepatitis suggests that these patients may have AIH type 1.

Anti-SLA antibodies may be detected in some patients with the primary biliary cirrhosis-AIH overlap syndrome, but not in healthy controls.

**Soluble Transferrin Receptor (sTfR), Serum**

**Clinical Information:** Iron uptake into cells is mediated through internalizing iron-transferrin complexes. The iron-transferrin complex binds to transferrin receptors present on the external face of the plasma membrane, and is internalized through endosomes with ultimate release of iron into the cytoplasm. Plasma membrane-bound transferrin receptor is released by proteolytic cleavage of the extracellular domain, resulting in the formation of a truncated soluble transferrin receptor (sTfR) that circulates freely in the blood. The concentration of sTfR is an indicator of iron status. Iron deficiency causes overexpression of transferrin receptor and sTfR levels, while iron repletion results in decreased sTfR levels. While ferritin measurement is the accepted method for assessment of iron deficiency, ferritin is an acute-phase reactant and elevates in response to processes that do not correlate with iron status, including inflammation, chronic disease, malignancy, and infection. sTfR is not an acute-phase reactant and the interpretation of iron status using sTfR measurement is not affected by these confounding pathologies.

**Useful For:** Evaluation of suspected iron deficiency in patients who may have inflammation, infection, or chronic disease and other conditions in which ferritin concentration does not correlate with iron status, including: -Cystic fibrosis patients who frequently have inflammation or infections(1-2) -Evaluating insulin-dependent diabetics who may have iron-deficiency resulting from gastric autoimmunity and atrophic gastritis(3)

**Interpretation:** Soluble transferrin receptor (sTfR) concentrations are inversely related to iron status; sTfR elevates in response to iron deficiency and decreases in response to iron repletion.

**Reference Values:**

1.8-4.6 mg/L

It is reported that African Americans may have slightly higher values.

**Clinical References:**
(OATP1B1) influx transporter located on the basolateral membrane of hepatocytes. OATP1B1 facilitates the hepatic uptake of statins as well as other endogenous compounds (eg, bilirubin). Changes in the activity of this transporter (eg, through genetic variations or drug-drug interactions) can increase the severity of statin-associated myopathy (ie, statin intolerance).(1) The most common adverse drug reaction associated with statins is skeletal muscle toxicity, which can include myalgia (with and without elevated creatine kinase levels), muscle weakness, muscle cramps, myositis, and rhabdomyolysis.(2) 

Rhabdomyolysis, while rare, is of clinical concern because of the risk for death as a result of cardiac arrhythmia, renal failure, and disseminated intravascular coagulation. While the underlying causes of statin-associated myopathy are not known, several hypotheses have been formulated, including those related to the biochemical pathway of cholesterol synthesis inhibition and statin metabolism. The SLC01B1*5 (c.521T>C, p.V174A; rs4149056) allele interferes with localization of the transporter to the plasma membrane, and can lead to increased systemic statin concentrations.(3) All statins are substrates of OATP1B1, but the association with SLC01B1*5 and statin intolerance varies depending on statin and dose, and is most pronounced with higher doses of simvastatin therapy. A case-control study of simvastatin-induced myopathy observed an odds ratio (OR) for myopathy of 4.5 per copy of the *5 allele in patients receiving high-dose (80 mg/day) simvastatin therapy (the OR was 16.9 in *5 homozygotes compared to individuals who did not carry *5).(4) Also demonstrated was a dose relationship in a replication cohort of patients taking 40 mg/day simvastatin with a relative risk of 2.6 per copy of the *5 allele. While SLC01B1 genotype has been shown to affect systemic exposure of other statins (eg, atorvastatin, pravastatin, rosuvastatin) in addition to simvastatin,(3) there is less evidence demonstrating a clinical association between SLC01B1 genotype and myopathy with statins other than simvastatin.(1) 

Frequency of the SLC01B1*5 allele varies across different racial and ethnic groups. The *5 allele occurs in the homozygous or heterozygous state in approximately 20% to 28% of Caucasians and Asians, and 8% of Africans.

**Useful For:** Aiding risk prediction for statin-associated myopathy in patients beginning statin therapy, especially simvastatin therapy Determining a potential genetic effect related to statin intolerance in patients with statin-associated myopathy, especially related to simvastatin

**Interpretation:** Heterozygosity and homozygosity for the SLC01B1*5 allele is associated with decreased organic anion-transporting polypeptide 1B1 (OATP1B1) activity and an increased risk for simvastatin-associated myopathy. Absence of the SLC01B1*5 allele decreases, but does not rule-out, the risk of simvastatin-associated myopathy. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
creatine kinase levels), muscle weakness, muscle cramps, myositis, and rhabdomyolysis. (2) Rhabdomyolysis, while rare, is of clinical concern because of the risk for death as a result of cardiac arrhythmia, renal failure, and disseminated intravascular coagulation. While the underlying causes of statin-associated myopathy are not known, several hypotheses have been formulated, including those related to the biochemical pathway of cholesterol synthesis inhibition and statin metabolism. The SLCO1B1*5 (c.521T>C, p.V174A; rs4149056) allele interferes with localization of the transporter to the plasma membrane, and can lead to increased systemic statin concentrations. (3) All statins are substrates of OATP1B1, but the association with SLCO1B1*5 and statin intolerance varies depending on statin and dose, and is most pronounced with higher doses of simvastatin therapy. A case-control study of simvastatin-induced myopathy observed an odds ratio (OR) for myopathy of 4.5 per copy of the *5 allele in patients receiving high-dose (80 mg/day) simvastatin therapy (the OR was 16.9 in *5 homozygotes compared to individuals who did not carry *5). (4) Also demonstrated was a dose relationship in a replication cohort of patients taking 40 mg/day simvastatin with a relative risk of 2.6 per copy of the *5 allele. While the SLCO1B1 genotype has been shown to affect systemic exposure of other statins (eg, atorvastatin, pravastatin, rosuvastatin), in addition to simvastatin, (3) there is less evidence demonstrating a clinical association between SLCO1B1 genotype and myopathy with statins other than simvastatin. (1) Frequency of the SLCO1B1*5 allele varies across different racial and ethnic groups. The *5 allele occurs in the homozygous or heterozygous state in approximately 20% to 28% of Caucasians and Asians, and 8% of Africans.

**Useful For:** Aiding risk prediction of statin-associated myopathy for patients beginning statin therapy, especially simvastatin therapy Determining a potential genetic effect related to statin intolerance in patients with statin-associated myopathy, especially related to simvastatin Genotyping patients who prefer not to have venipuncture done

**Interpretation:** Heterozygosity and homozygosity for the SLCO1B1*5 allele is associated with decreased organic anion-transporting polypeptide 1B1 (OATP1B1) activity and an increased risk for simvastatin-associated myopathy. Absence of the SLCO1B1*5 allele decreases, but does not rule out, the risk of simvastatin-associated myopathy. For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Somatostatin**

**Clinical Information:** Somatostatin is a cyclic peptide originally isolated from sheep hypothalami and shown to inhibit the release of Growth Hormone. Somatostatin is present primarily in three main forms: a 14 amino acid peptide, a 28 amino acid peptide (Big Somatostatin), and a 12,000 molecular weight Pro-Somatostatin. This assay measures only the 14 amino acid form of Somatostatin. All three forms of Somatostatin have similar biological properties and overall potencies. Somatostatin is a physiological regulator of islet cell and gastrointestinal functions, and is a suppressor of many pituitary hormones including Growth Hormone, Prolactin, and Thyrotropin (TSH). Somatostatin levels are often elevated in diabetics, but the levels return to normal upon correction of the hormonal and metabolic deficiencies present. In many cases of APUDomas including VIPoma, Insulinoma, Glucagonoma, and Gastrinoma, elevated levels of Somatostatin are found.

**Reference Values:**

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

**SOS1 Gene, Known Mutation, Blood**

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-MAPK pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 approximately 10%, and KRAS less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in up to 30% to 75% of families. The SOS1 gene comprises 23 exons and encodes a 150-kd autoinhibited RAS-specific guanine nucleotide exchange factor. After receptor tyrosine kinase (RTK) stimulation, SOS1 is recruited to the plasma membrane, where it acquires a catalytically active conformation and catalyzes activation of the Ras-MAPK pathway. Reported NS-associated mutations in SOS1 are missense, gain-of-function mutations and are believed to abolish autoinhibition, which leads to increased and prolonged Ras activation. In addition to Noonan syndrome and related phenotypes, an insertion mutation in SOS1 that creates a premature stop codon at residue 1106 was identified in an extensive Brazilian family with hereditary gingival fibromatosis, an overgrowth condition characterized by a benign, slowly progressive, nonhemorrhagic, fibrous enlargement of maxillary and mandibular keratinized gingiva. Genetic testing for SOS1 mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

**Useful For:** Genetic testing of individuals at risk for a known SOS1 mutation that has been identified in a family member

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

SOS1F
34602

SOS1, Full Gene Sequence

Reference Values:
Only orderable as part of a profile. For further information see SOS1 / SOS1, Full Gene Sequence, Blood.

SOS1
89467

SOS1, Full Gene Sequence, Blood

Clinical Information: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. There is no apparent prevalence in any particular ethnic group. Several syndromes have overlapping features with NS, including cardiofaciocutaneous (CFC), Costello, Williams, Aarskog, and LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndromes. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous mutations in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway, the Ras-MAPK pathway, which is important for cell growth, differentiation, senescence, and death. Molecular genetic testing identifies PTPN11 mutations in 50% of individuals. Mutations in RAF1 are identified in approximately 3% to 17%, SOS1 approximately 10%, and KRAS less than 5% of affected individuals. NS can be sporadic and due to new mutations; however, an affected parent can be recognized in up to 30% to 75% of families. The SOS1 gene comprises 23 exons and encodes a 150-kd autoinhibited RAS-specific guanine nucleotide exchange factor. After receptor tyrosine kinase (RTK) stimulation, SOS1 is recruited to the plasma membrane, where it acquires a catalytically active conformation and catalyzes activation of the Ras-MAPK pathway. Reported NS-associated mutations in SOS1 are missense, gain-of-function mutations and are believed to abolish autoinhibition, which leads to increased and prolonged Ras activation. In addition to NS and related phenotypes, an insertion mutation in SOS1 that creates a premature stop codon at residue 1106 was identified in an extensive Brazilian family with hereditary gingival fibromatosis, an overgrowth condition characterized by a benign, slowly progressive, nonhemorrhagic, fibrous enlargement of maxillary and mandibular keratinized gingiva. Genetic testing for SOS1 mutations can allow for the confirmation of a suspected genetic disease. Confirmation of NS or other associated phenotypes allows for proper treatment and management of the disease and preconception, prenatal, and family counseling.

Useful For: Aiding in the diagnosis of SOS1-associated Noonan syndrome and hereditary gingival fibromatosis

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.


FSOTA 91123
Sotalol (Betapace)
Reference Values:
Reference Range:  500 - 4000 ng/mL

Serum Sotalol concentrations producing beta-blockade:
500 - 4000 ng/mL

Toxic range has not been established.

FSOYG 57551
Soybean IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Reference Values: < 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FSYG4 57574
Soybean IgG4
Interpretation: mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

Reference Values: <0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

SOY 82886
Soybean, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Special Red Cell Antigen Typing

Clinical Information: The presence or absence of a cellular antigen is an inherited trait. As a general rule, individuals will not make antibody directed against an antigen present on their own red blood cells.

Useful For: Added proof of alloantibody specificity Determining possible antibody specificities in complex cases This test is not done for the purpose of establishing paternity

Interpretation: Each antigen typed will be listed by name, followed by "pos" indicating that the antigen is present, or by "neg" indicating that the antigen is absent.

Specific Gravity, Body Fluid

Clinical Information: Specific gravity (SG), the ratio of the mass of a solution compared to the mass of an equal volume of water, is an estimate of the concentration of substances dissolved in the solution. Accessing whether a body fluid specimen is exudative or transudative in nature is the initial step in determining the etiology of the fluid. Transudative fluids result from hemodynamic aberrations or oncotic changes and are associated with ultrafiltration of serum across membranes. Transudates most commonly occur in association with clinically apparent conditions such as heart failure and cirrhosis. Exudative fluids tend to develop as a consequence of inflammation or malignant disorders such as tuberculosis, pneumonia or cancer, in which capillary permeability is increased, allowing large-molecular-weight compounds to be released into the accumulating fluid. If the fluid is transudate, further diagnostic procedures are often not necessary, however the presence of an exudative fluid often triggers additional testing that may be invasive in nature. Determination of body fluid SG can aid in the distinction between transudative and an exudative fluid. SG in exudates is greater than in transudates. This same information can be obtained from the total protein using 3 g/dL as the cutoff.

Useful For: An aid in determining the type of body fluid: exudate versus transudate

Interpretation: Exudate fluid specific gravity (SG) is >1.015; transudate fluid SG is <1.015

Reference Values: No established reference values


Specific Gravity, Urine

Clinical Information: Specific gravity (SG), the ratio of the mass of a solution compared to the mass of an equal volume of water, is an estimate of the concentration of substances dissolved in the solution. Urine SG can be used to assess the kidney’s ability to concentrate or dilute urine. However, because protein, glucose, and contrast dye have molecular masses that are relatively large compared to other major components of urine (e.g., sodium, chloride, potassium), they disproportionately affect SG. In these cases, urine osmolality is a better measure of urine concentration.

Useful For: As a partial assessment of the kidney’s ability to concentrate urine

Interpretation: Low specific gravity (SG) (1.001-1.003) may indicate the presence of diabetes insipidus, a disease caused by impaired functioning of antidiuretic hormone (ADH). Low SG also may occur in patients with glomerulonephritis, pyelonephritis, and other renal abnormalities. In these cases the kidney has lost its ability to concentrate due to tubular damage. High SG may occur in patients with adrenal insufficiency, hepatic disease, congestive heart failure, or in patients experiencing excessive water loss due to sweating, fever, vomiting, or diarrhea.

Reference Values: 1.002-1.030


Specimen Source Identification

Clinical Information: For various reasons, the patient origin for a particular specimen may be questioned. This is especially true for paraffin-embedded material: labeling accuracy may be questioned or tissue from other sources may be included by mistake. Confirmation of the patient origin may be critical to the clinical workup of that patient. Molecular methods are now available to extract DNA from
various sources, including paraffin-embedded material, and to compare the molecular fingerprint (genotype) of one specimen source with another one. Matching genotypes on multiple specimens suggest that they are derived from the same patient, whereas differences in genotype suggest different patient sources.

**Useful For:** Determining specimen origin when the patient identity of a specimen is in question

**Interpretation:** An interpretive report will be provided.


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**Spinach IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Spinach, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Range</td>
<td>Interpretation</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>3 3.50-17.4</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
<td></td>
</tr>
<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
<td></td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
<td></td>
</tr>
</tbody>
</table>


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**FSMAC 57189**

**Spinal Muscular Atrophy Carrier Test**

**Reference Values:**
Testing is complete. Report has been attached in MayoAccess.

**FSMA 91591**

**Spinal Muscular Atrophy Diagnostic Test**

**Reference Values:**
Testing is complete. Report has been attached in MayoAccess.

**SPNKZ 35554**

**SPINK1 Gene, Full Gene Analysis**

**Clinical Information:** Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic, or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. The most common monogenic cause of hereditary pancreatitis, in which a single gene mutation confers major risk susceptibility to chronic pancreatitis, is the presence of a mutation in the PRSS1 gene. Biallelic mutations in the SPINK1 gene have also been associated with increased susceptibility to chronic pancreatitis, especially in families without PRSS1 mutations. However, it is currently unknown if biallelic mutations alone are sufficient to cause chronic pancreatitis if other risk factors are required for disease expression. Additionally, heterozygous SPINK1 mutations appear to modify disease severity when observed in combination with mutations in other genes. Unlike PRSS1 mutations, SPINK1 mutations have been associated with alcohol-induced and tropical pancreatitis. Genetic testing for all 4 pancreatitis susceptibility genes, including SPINK1, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

**Useful For:** Identification of gene mutations contributing to pancreatitis in an individual or family

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


Spinobulbar Muscular Atrophy (Kennedy Disease), Molecular Analysis

**Clinical Information:** X-linked spinal and bulbar muscular atrophy (spinobulbar muscular atrophy: SBMA; or Kennedy disease) is characterized by onset of progressive muscle weakness, atrophy, and fasciculations typically in the fourth or fifth decade of life. Affected patients also have signs of androgen insensitivity such as gynecomastia, reduced fertility, and testicular atrophy. The clinical severity and age at onset can be quite variable, even within families. Because this is an X-linked disease, males manifest this disorder and females are generally asymptomatic carriers. However, there have been reports of female carriers who exhibit symptoms such as muscle weakness and cramping. SBMA is caused by an expansion of the CAG trinucleotide repeat in exon 1 of the human androgen receptor (AR) gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 11 to 34. The number of repeats found in affected individuals can range from 38 to 62. There is no consensus as to the clinical significance of alleles of 35 CAG repeats and literature suggests that alleles of 36 to 37 CAG repeats may be associated with reduced penetrance. As with other trinucleotide repeat disorders, anticipation is frequently observed and larger CAG expansions are associated with earlier onset and a more rapid clinical progression.

**Useful For:** Molecular confirmation of clinically suspected cases of sporadic or familial spinobulbar muscular atrophy (SBMA) Presymptomatic testing for individuals with a family history of SBMA and a documented expansion in the androgen receptor (AR) gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles: 11-34 CAG repeats
Abnormal alleles: 36-62 CAG repeats

An interpretive report will be provided.


Sporothrix Antibody, Serum

**Clinical Information:** Sporotrichosis is an endemic fungal infection caused by the dimorphic fungus Sporothrix schenckii. Most cases of sporotrichosis have been reported from the subtropical and tropical regions of the Americas, but a global distribution is likely. The organism is often isolated from soil, plants, or plant products (wood), and occupational or recreational exposure to these materials is often implicated in infected individuals. Infections due to Sporothrix schenckii can be differentiated into several distinct syndromes: -The cutaneous form of the disease is most common, often arising from sites of minor skin trauma. The primary erythematous, papulonodular lesion may range from several millimeters to 4 cm in size. Secondary lesions develop proximally along lymphatic channels. These generally painless lesions usually do not involve lymph nodes, although lymphadenopathy may develop. -Extracutaneous sporotrichosis can be manifested as osteoarticular involvement of a single joint. Major joints of the extremities (ankle, knee, elbow, hand) are most often involved. The affected joint is swollen and painful, with an attendant effusion. Systemic symptoms are minimal. -Pulmonary sporotrichosis with cavitary lesions also has been described. -A multifocal extracutaneous syndrome has been described, consisting of multijoint involvement, or widely scattered cutaneous lesions. Constitutional symptoms (fever, weight
loss) are often noted, and spread to bone and central nervous system may occur. Underlying immune system suppression is often a contributing factor. Untreated infection is ultimately fatal. (1)

**Useful For:** Aiding in the diagnosis of extracutaneous sporotrichosis

**Interpretation:** Extracutaneous infections, including disseminated and articular infections, produce positive tests. The test should be positive in approximately 90% to 95% of all primary sporotrichosis infections. Specimens from these patients may become positive by 2 weeks after infection and are not expected to remain positive for more than 7 months after the original primary infection. Agglutination titers of $\geq 1:8$ indicate presumptive evidence of sporotrichosis. Titers of 1:4 to 1:8 are commonly seen in normal persons. Some cutaneous infections are associated with negative serologic results.

**Reference Values:**

Negative

**Clinical References:**


---

**Sporothrix Antibody, Spinal Fluid**

**Clinical Information:** Sporotrichosis is an endemic fungal infection caused by the dimorphic fungus Sporothrix schenckii. Most cases of sporotrichosis have been reported from the subtropical and tropical regions of the Americas, but a global distribution is likely. The organism is often isolated from soil, plants, or plant products (wood), and occupational or recreational exposure to these materials is often implicated in infected individuals. Infections due to Sporothrix schenckii can be differentiated into several distinct syndromes: -The cutaneous form of the disease is most common, often arising from sites of minor skin trauma. The primary erythematous, papulonodular lesion may range from several millimeters to 4 cm in size. Secondary lesions develop proximally along lymphatic channels. These generally painless lesions usually do not involve lymph nodes, although lymphadenopathy may develop. -Extracutaneous sporotrichosis can be manifested as osteoarticular involvement of a single joint. Major joints of the extremities (ankle, knee, elbow, hand) are most often involved. The affected joint is swollen and painful, with an attendant effusion. Systemic symptoms are minimal. -Pulmonary sporotrichosis with cavitary lesions also has been described. -A multifocal extracutaneous syndrome has been described, consisting of multijoint involvement, or widely scattered cutaneous lesions. Constitutional symptoms (fever, weight loss) are often noted, and spread to bone and central nervous system may occur. Underlying immune system suppression is often a contributing factor. Untreated infection is ultimately fatal. (1)

**Useful For:** Aiding in the diagnosis of extracutaneous sporotrichosis

**Interpretation:** Any titer should be considered clinically significant, however, clinical correlation must be present. Extracutaneous infections, including disseminated and articular infections, produce positive tests.

**Reference Values:**

Negative

**Clinical References:**


---

**Spotted Fever Group Antibody, IgG and IgM, Serum**

**Clinical Information:** Species of Rickettsia are small (0.3-0.5 mcm x 1-2 mcm) obligately intracellular bacteria (Proteobacteria). They have a gram-negative cell wall structure. Rickettsia are found in arthropod hosts for at least part of their life cycle. Rickettsial infections in the United States are caused...
by 2 major groups within the genus Rickettsia: spotted fever group and typhus fever group. The spotted fever group includes Rickettsia rickettsii (Rocky Mountain spotted fever), Rickettsia akari, Rickettsia conorii (Boutonneuse fever), Rickettsia australis (Queensland tick typhus), and Rickettsia sibirica (North Asian tick typhus). The typhus fever group includes Rickettsia typhi (murine typhus; endemic typhus), and Rickettsia prowazekii (epidemic typhus). Rickettsia rickettsiae is the most common rickettsial species encountered in the United States and is transmitted through a tick vector (Dermacentor species or, less commonly, Rhipicephalus sanguineus). Following a 2- to 14-day incubation period, patients most commonly present with fever, chills, and myalgia. A maculopapular rash typically appears 2 to 5 days after fever onset, though approximately 10% of patients will not develop a rash. Antibodies to the spotted fever group agents are detectable within 7 to 10 days after illness onset. Demonstration of either 1) seroconversion or 2) a 4-fold change in IgG specific antibody titers in acute and convalescent serum samples is consistent with acute or ongoing disease.

**Useful For:** An aid in the diagnosis of spotted fever group rickettsial infections

**Interpretation:** This test detects reactivity to the group-specific rickettsia. For example, antibody reactivity to the Rickettsia rickettsii will also react with other organisms within the spotted fever group. IgG > or =1:256: -Serum end point titers of > or =1:256 are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. <1:256 and > or =1:64: -Single serum end point titers > or =1:64 and <1:256 are suggestive of infection at an undetermined time and may indicate either past infection or early response to a recent rickettsial infection. -A 4-fold or greater increase in IgG titer between 2 serum specimens drawn 1 to 2 weeks apart and tested in parallel is considered presumptive evidence of a recent or current infection. -In patients infected with organisms within the rickettsial groups, IgG antibody is generally detectable within 1 to 2 weeks of onset of symptoms, peaking within 1 to 2 months, and declining thereafter. Following prompt antimicrobial treatment, titers generally decline below detectable levels within 8 to 11 months. With relapse, prior immunization, or delayed antibiotic treatment, IgG levels may remain elevated for more than a year post-onset. IgM > or =1:64: -Titors of > or =1:64 are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. <1:64: -Titors <1:64 suggest that the patient does not have an acute rickettsial infection. -IgM class antibody is transiently detected within 1 to 2 weeks of onset of symptoms, usually declining rapidly within 3 months following prompt antibiotic treatment. These levels will also be elevated for an extended period with relapse, prior immunization, or delayed antibiotic treatment.

**Reference Values:**

IgG: <1:64

IgM: <1:64


### Spruce, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3.50-17.4</td>
<td>Positive</td>
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Reference values apply to all ages.


**FSCC 57312**

**Squamous Cell Carcinoma Antigen, Serum**

**Reference Values:**

0.0 - 2.2 ng/mL

SCC antigen levels alone should not be interpreted as evidence of the presence or absence of malignant disease. In patients with known or expected cancer, other tests and procedures must be considered for diagnosis and patient management. Results obtained with different assay methods or kits cannot be used interchangeably.

**SQUA 82797**

**Squash, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Reference Values:**

Values apply to all ages.


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**FSRP**

**Interpretation:** Signal Recognition Particle (SRP) is a myositis specific autoantibody which is seen in 5-10% of adult and juvenile myositis. Symptoms often are acute onset of severe polymyositis with frequent myalgias, severe weakness and very high creatine kinase levels. Some adults experience cardiac involvement and palpitations. There is a poor response to therapy.

**Reference Values:**

Negative

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**SSAB**

**Clinical Information:** SS-A/Ro, SS-B/La, RNP, and Sm are autoantigens commonly referred to as extractable nuclear antigens (ENAs). Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases). SS-A/Ro is composed of protein antigens of 52kD and 60 kD combined with cytoplasmic RNA species. SS-A/Ro antibodies occur in patients with several different connective tissue diseases including Sjogren's syndrome, an autoimmune disease that involves primarily the salivary and lachrymal glands (up to 90% of cases); lupus erythematosus (LE) (40%-60% of cases); and rheumatoid arthritis. SS-A/Ro antibodies are associated with childhood LE, neonatal LE, and with congenital heart block in infants born to mothers with LE.(1,2) SS-A/Ro antibodies have also been reported to be associated with features of extravascular inflammation in patients with LE including vasculitis, purpura, cytopenias, and adenopathy. SS-B/La is composed of a 48-kD protein combined with RNA species. SS-B/La antibodies are found primarily in patients with Sjogren's syndrome or LE, where they occur with frequencies of approximately 60% and 15%, respectively.(1,2) SS-B/La antibodies occur only infrequently in the absence of SS-A/Ro antibodies. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive, especially those with signs and symptoms consistent with Sjogren's syndrome or lupus erythematosus

**Interpretation:** A positive result for SS-A/Ro or SS-B/La antibodies is consistent with connective tissue disease, including Sjogren's syndrome, lupus erythematosus (LE), or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with LE prior to delivery indicates an increased risk of congenital heart block in the neonate.

**Reference Values:**

SS-A/Ro ANTIBODIES, IgG

<1.0 U (negative)
SS-A/Ro Antibodies, IgG, Serum

Clinical Information: SS-A/Ro is an extractable nuclear antigen (ENA) composed of protein antigens of 52 kD and 60 kD combined with cytoplasmic RNA species. SS-A/Ro antibodies occur in patients with several different connective tissue diseases including Sjogren syndrome, an autoimmune disease that involves primarily the salivary and lachrymal glands (up to 90% of cases); lupus erythematosus (LE) (40%–60% of cases); and rheumatoid arthritis. SS-A/Ro antibodies are associated with childhood LE, neonatal LE, and with congenital heart block in infants born to mothers with LE. SS-A/Ro antibodies have also been reported to be associated with features of extraglandular inflammation in patients with LE including vasculitis, purpura, cytopenias, and adenopathy. SS-A/Ro is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENAs). The other ENAs are SS-B/La, RNP, and Sm. Each ENA is composed of 1 or more proteins associated with small nuclear or cytoplasmic RNA species (snRNP) ranging in size from 80 to 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive.

Interpretation: A positive result for SS-A/Ro antibodies is consistent with connective tissue disease, including Sjogren syndrome, lupus erythematosus (LE), or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with LE prior to delivery indicates an increased risk of congenital heart block in the neonate.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


SS-B/La Antibodies, IgG, Serum

Clinical Information: SS-B/La is an extractable nuclear antigen (ENA) composed of a 48-kD protein combined with RNA species. SS-B/La antibodies are found primarily in patients with Sjogren’s syndrome or lupus erythematosus (LE), where they occur with frequencies of approximately 60% and
15%, respectively.(1,2) SS-B/La antibodies occur only infrequently in the absence of SS-A/Ro antibodies. SS-B/La is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENAs). The other ENAs are SS-A/Ro, RNP, and Sm. Each ENA is composed of 1 or more proteins associated with cytoplasmic or small nuclear RNA species (snRNP) ranging in size from 80 to 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren's syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care; The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive result for SS-B/La antibodies is consistent with connective tissue disease, including Sjogren’s syndrome and lupus erythematosus.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:**

---

**St. Louis Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid**

**Clinical Information:** Since 1933, outbreaks of St. Louis encephalitis (SLE) have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Infections with arboviruses, including SLE, can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. SLE tends to produce the most severe clinical infections in older persons.

**Useful For:** Aiding the diagnosis of St. Louis encephalitis

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:**
St. Louis Encephalitis Antibody, IgG and IgM, Serum

Clinical Information: Onset is characterized by generalized malaise, fever, chilliness, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by the meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Areas of outbreaks since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence of St. Louis encephalitis is associated with summer and early autumn.

Useful For: Aiding in the diagnosis of St. Louis encephalitis

Interpretation: In patients with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG > or =1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. Infections with St. Louis encephalitis can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age: St. Louis encephalitis tends to produce the most severe clinical infections in older persons. Infection among males is primarily due to working conditions and sports activity taking place where the vector is present.

Reference Values:
IgG: <1:10
IgM: <1:10


ST2, Serum

Clinical Information: Heart failure is a chronic, progressive, complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are readmitted within the forthcoming year, incurring costly treatments and therapies.(1) The development and progression of heart failure is a clinically silent process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury or stress.(2) Soluble ST2 is a biomarker that appears to be actively involved with IL-33 in modulating cardiac remodeling and ventricular function via effects in the inflammatory and apoptosis pathways.(3) ST2 is a member of the interleukin-1 receptor family and has 2 isoforms that are directly implicated in progression of cardiac disease: soluble ST2 (sST2) and a transmembrane-bound form, ST2 ligand (ST2L). IL-33 is the hormone that interacts with ST2L, protecting against left ventricular hypertrophy and myocardial fibrosis to effectively preserve cardiac function. Therefore, when sST2 concentrations are high, IL-33 is...
unavailable for cardioprotective signaling, leaving the heart vulnerable to the effects of sST2. High concentrations of sST2 result in cellular death, tissue fibrosis, reduced cardiac function, and an increase in the rate of disease progression.

**Useful For:** Aiding in prognosis for patients diagnosed with chronic heart failure

**Interpretation:** Clinically, ST2 concentrations in the HF-ACTION heart failure study were a significant predictor of mortality, all-cause hospitalization, mortality due to cardiovascular disease, and hospitalization due to cardiovascular disease using a cutpoint of 35 ng/mL. In addition, mortality risk was significantly higher in patients with ST2 >35 ng/mL.(4) The risk appears early and persists throughout the follow-up period. Clinical risk categories are substantiated by results from several large chronic heart failure studies: - Low risk: < or =35.0 ng/mL - High risk: >35.0 ng/mL (high risk) Results should be interpreted in the context of the individual patient presentation. Elevated ST2 results indicate an increased risk for adverse outcomes and signal the adverse remodeling and progression of disease. The reference interval was derived from normal donors without a history of cardiovascular disease, stroke, diabetes, renal disease, liver disease, or autoimmune diseases. The reference range is gender dependent; however, it is the clinical cutpoint that is recognized as providing the most utility. Knowledge of ST2 results in a heart failure patient may assist in cardiovascular risk stratification and lead to more aggressive management. There are no specific ST2 inhibitors available at this time and heart failure patients with elevated ST2 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers (ARBs) and aldosterone antagonists are thought to be particularly effective.

**Reference Values:**

Males:
- <18 years: not established
- > or =18 years: < or =52.0 ng/mL

Females:
- <18 years: not established
- > or =18 years: < or =38.7 ng/mL

**Stachybotrys chartarum/atra IgA:** <1.0 mg/L

**Stemphyllium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Reference values apply to all ages.**


**Steroid Sulfatase Deficiency, Xp22.3 Deletion, FISH**

**Clinical Information:** This test is appropriate in individuals with clinical features suggestive of X-linked ichthyosis and carrier testing for women with a family history of X-linked ichthyosis. Steroid sulfatase deficiency syndrome is associated with a deletion of the STS gene on the short arm of X chromosome (Xp22.3). The syndrome is an X-linked form of ichthyosis, which is a group of cutaneous disorders characterized by increased or abnormal keratinization. The phenotype is variable, with affected males presenting with dry and scaly skin, sparse hair, and conical teeth. Steroid sulfatase catalyzes the conversion of sulfated steroid precursors to estrogens during pregnancy. Prenatal specimens may be tested in cases where maternal serum screening has identified low or absent levels of unconjugated estriol.
Female relatives of affected males carry the deletion and should be tested if an affected male has been identified.

**Useful For:** Establishing a diagnosis of X-linked ichthyosis syndrome Detecting cryptic rearrangements involving Xp22.3 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern (1 signal on the X homolog) in each metaphase is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Sterols, Plasma**

**Clinical Information:** Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play an important role in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysomorphic facial features, psychomotor retardation, and failure to thrive. The clinical phenotype of desmosterolosis (desmosterol reductase deficiency) is similar to Smith-Lemli-Opitz (SLO) syndrome (7-dehydrocholesterol reductase deficiency) and typically involves the central nervous system (CNS). Its biochemical marker is the elevation of desmosterol in plasma, tissue, and cultured cells. Sitosterolemia is a rare autosomal recessive disorder caused by mutations in the ATP-binding cassette (ABC) transporter genes, ABCG5 and ABCG8, which abnormally enhance the absorption of plant sterols and cholesterol from the intestines. Patients often present with hematologic abnormalities and tendon and tuberous xanthomas as well as premature coronary artery disease. A biochemical diagnosis of sitosterolemia is made by documenting elevations of the plant sterols sitosterol and campesterol in plasma or serum.

**Useful For:** Investigation of possible desmosterolosis (desmosterol reductase deficiency) and sitosterolemia

**Interpretation:** A quantitative report of the patient's sterol profile and a Biochemical Genetics consultant's interpretation is provided for each specimen.

**Reference Values:**
- DESMOSTEROL
  - 0.0-5.0 mg/L
- LATHOSTEROL
  - 0.0-7.0 mg/L
- CAMPESTEROL
  - 0.0-7.0 mg/L
- SITOSTEROL
  - 0.0-5.0 mg/L

**Clinical References:**
1. FitzPatrick DR, Keeling JW, Evans MJ, et al: Clinical phenotype of
INSEC
31765

Stinging Insects Allergen Profile

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effectors (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


STKZ
35556

STK11 Gene, Full Gene Analysis

Current as of July 8, 2016 11:28 am CDT
**Clinical Information:** Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by gastrointestinal (GI) hamartomatous polyps and melanotic macules. The GI polyps are most common in the small intestine. Although typically benign, these polyps can cause chronic bleeding and may result in obstruction and intussusception. Pigment changes, typically dark blue spots around the lips, buccal mucosa, and fingers, appear in childhood. Affected individuals are also at an increased risk for a variety of malignancies including colorectal, gastric, breast, thyroid, pancreatic, uterine, and sertoli cell and sex cord tumors. PJS is caused by mutations in the STK11 (formerly LKB1) gene.

**Useful For:** Confirming a diagnosis of Peutz-Jeghers syndrome

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FSTBG 57656**

**Strawberry IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**STBY 82676**

**Strawberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Streptococcal Antibodies Profile**

**Clinical Information:** A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

**Useful For:** Demonstration of acute or recent streptococcal infection

**Interpretation:** Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests; a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test such as anti-DNase B is recommended.

**Reference Values:**

ANTISTREP-O TITER
ANTI-DNase B TITER

<5 years: \(< \text{ or } = 250 \text{ U/mL}

5-17 years: \(< \text{ or } = 375 \text{ U/mL}

> or =18 years: \(< \text{ or } = 300 \text{ U/mL}


Streptococcus pneumoniae Antigen, Spinal Fluid

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia, and can also be an agent of bacterial meningitis. Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are being considered prior to culture confirmation, antigen testing may be useful. Note: According to the College of American Pathologists (CAP, IMM.41830), cerebrospinal fluid (CSF) samples collected to make an initial diagnosis and submitted for detection of Streptococcus pneumoniae antigen testing should also be submitted for routine bacterial culture. Mayo Medical Laboratories recommends that CSF bacterial cultures be performed at the originating site.

Useful For: Rapid diagnosis of pneumococcal meningitis

Interpretation: A positive result supports a diagnosis of pneumococcal meningitis. A negative result suggests that pneumococcal antigen is absent in the cerebrospinal fluid (CSF). However, infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the lower limit of detection of the test. If pneumococcal meningitis is suspected, bacterial culture and Gram-stain analysis on CSF should be performed.

Reference Values:

Negative


Streptococcus pneumoniae Antigen, Urine

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia (CAP). Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are provided for CAP without culture confirmation of Streptococcus pneumoniae, antigen testing may be useful.

Useful For: Rapid diagnosis of pneumococcal pneumonia

Interpretation: A positive result is indicative of pneumococcal pneumonia. A negative result is a presumptive negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the detection limit of the test. Pneumococcal pneumonia is best diagnosed by sputum culture.

Reference Values:
Negative


**Streptococcus pneumoniae IgG Antibodies, 23 Serotypes, Serum**

**Clinical Information:** Streptococcus pneumoniae is a gram-positive bacteria that causes a variety of infectious diseases in children and adults, including invasive disease (bacteremia and meningitis) and infections of the respiratory tract (pneumonia and otitis media). In 2009, it is estimated that Streptococcus pneumoniae was responsible for approximately 43,500 infections and 5,000 deaths in the United States. More than 90 serotypes of Streptococcus pneumoniae have been identified, based on varying polysaccharides that are found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune. Vaccines containing bacterial polysaccharides can be effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma and memory B cells, which can protect an individual against bacterial disease. Active immunization of adults and children >2 years is performed with nonconjugated polysaccharide vaccines (Pneumovax and Pnu-Immune 23) that contain a total of 23 serotypes, namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Antibody responses develop in approximately 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization. Immunization with a 23-valent vaccine is recommended for all adults > or =65 years of age and for adults 18 to 64 years of age with certain chronic diseases (heart disease, lung disease, type I diabetes, liver disease), those who are immunocompromised (congenital or acquired immunodeficiencies, malignancy, solid-organ transplant), and those with functional or anatomic asplenia. In contrast to adults and older pediatrics, immune responses to polysaccharide antigens in children <2 years of age are generally weak. Active immunization of children <2 years requires multiple injections of vaccine prepared from purified polysaccharides conjugated to an immunogenic carrier (Corynebacterium diphtheria strain C7 protein), which results in a T-cell dependent antibody response. Prior to the availability of routine Streptococcus pneumoniae vaccination, in children <6 years, 7 serotypes (4, 6B, 9V, 18C, 19F, and 23F) accounted for 80% of invasive disease and up to 100% of all isolates that were found to be highly resistant to treatment with penicillin. The first conjugated vaccine available for children <2 years (Prevnar) contained these 7 serotypes. The vaccine was highly effective, with invasive disease in children less than 5 years of age reduced from 99 to 21 cases per 100,000 population from 1998 to 2008. In addition, it was demonstrated that, after Prevnar became part of the routine vaccination schedule, only 2% of invasive disease was associated with any of the serotypes present in the 7-valent conjugate vaccine. Instead, approximately 61% of the invasive disease was caused by an additional 6 serotypes, including 1, 3, 5, 6A, 7F, and 19A. This led to development of a 13-valent Streptococcus pneumoniae polysaccharide conjugate vaccine, which is marketed as Prevnar13. Prevnar13 is approved for administration to all children ages 6 weeks to 71 months, and has replaced the previous 7-valent Prevnar vaccine. Patients with intrinsic defects in humoral immunity, such as common variable immunodeficiency, may have impaired antibody responses to pneumococcal vaccination. Further, impaired polysaccharide responsiveness, also known as selective antibody deficiency, is a recognized clinical entity in patients >2 years and is characterized by recurrent bacterial respiratory infections, absent or subnormal antibody response to a majority of the polysaccharide antigens, and normal or increased immunoglobulin levels, including IgG subclasses, in the context of an intact humoral response to protein antigens. In several other primary immunodeficiencies, including Wiskott-Aldrich syndrome, autoimmune lymphoproliferative syndrome, and DiGeorge syndrome, IgG subclass deficiencies may also result in impaired antibody responses to polysaccharide antigens.

**Useful For:** Assessing the IgG antibody response to active immunization with nonconjugated, 23-valent vaccines Assessing the IgG antibody response to active immunization with conjugated, 13-valent vaccines Determining the ability of an individual to produce an antibody response to
polysaccharide antigen(s), as part of an evaluation for humoral or combined immunodeficiencies.

**Interpretation:** As a general guideline, nonimmunocompromised adults develop IgG antibodies approximately 4 to 6 weeks following nonconjugated vaccination. A study conducted at the Mayo Clinic assessed IgG antibody concentrations prior to and following vaccination in a cohort of 100 healthy adults who met stringent exclusion criteria, including lack of previous pneumococcal vaccination or pneumonia associated with Streptococcus pneumoniae infection. Based on this data, reference ranges were established that most effectively discriminated between prevaccination and postvaccination antibody concentrations. Antibody concentrations greater than or equal to the reference value for at least 50% of serotypes in either a pre- or postvaccination specimen or a 2-fold or greater increase in antibody concentrations for at least 50% of serotypes when comparing the pre- to the postvaccination results would be consistent with a normal response to Streptococcus pneumoniae vaccination. Serotype-specific antibodies may persist for up to 10 years following immunization or infection.

**Reference Values:**

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
<td>&gt; or =2.3</td>
</tr>
<tr>
<td>2 (2)</td>
<td>&gt; or =1.0</td>
</tr>
<tr>
<td>3 (3)</td>
<td>&gt; or =1.8</td>
</tr>
<tr>
<td>4 (4)</td>
<td>&gt; or =0.6</td>
</tr>
<tr>
<td>5 (5)</td>
<td>&gt; or =10.7</td>
</tr>
<tr>
<td>8 (8)</td>
<td>&gt; or =2.9</td>
</tr>
<tr>
<td>9N (9)</td>
<td>&gt; or =9.2</td>
</tr>
<tr>
<td>12F (12)</td>
<td>&gt; or =0.6</td>
</tr>
<tr>
<td>14 (14)</td>
<td>&gt; or =7.0</td>
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<td>17F (17)</td>
<td>&gt; or =7.8</td>
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<td>19F (19)</td>
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<td>20 (20)</td>
<td>&gt; or =1.3</td>
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<td>22F (22)</td>
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<td>23F (23)</td>
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</tr>
<tr>
<td>10A (34)</td>
<td>&gt; or =2.9</td>
</tr>
<tr>
<td>11A (43)</td>
<td>&gt; or =2.4</td>
</tr>
<tr>
<td>7F (51)</td>
<td>&gt; or =3.2</td>
</tr>
<tr>
<td>15B (54)</td>
<td>&gt; or =3.3</td>
</tr>
<tr>
<td>18C (56)</td>
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</tr>
<tr>
<td>19A (57)</td>
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</tr>
<tr>
<td>9V (68)</td>
<td>&gt; or =2.6</td>
</tr>
<tr>
<td>33F (70)</td>
<td>&gt; or =1.7</td>
</tr>
</tbody>
</table>

**Clinical References:**

5. Paradiso PR: Advances in pneumococcal
FSTSC
91984
Streptozyme Screen with Reflex to Titer

Reference Values:
Negative

STR
8746
Striational (Striated Muscle) Antibodies, Serum

Clinical Information: Autoantibodies directed against the contractile elements of striated muscle are found in 30% of adult patients with myasthenia gravis and in 80% of those with thymoma. These antibodies may also be detected in patients with: Lambert-Eaton myasthenic syndrome, small-cell lung carcinoma, breast carcinoma, patients treated with D-penicillamine, bone marrow transplant recipients having graft-versus-host disease, and autoimmune liver disorders. While this test is used as a serological aid in the diagnosis of thymoma, especially in patients with onset of myasthenia gravis (MG) younger than 45 years, it is more predictive of thymoma when accompanied by a muscle acetylcholine receptor (AChR) modulating antibody value of > or = 90% AChR loss and is most predictive of thymoma when accompanied by CRMP-5-IgG. Serial measurements are useful after treatment of thymoma. Measurements of muscle AChR binding, muscle AChR modulating antibody, and CRMP-5-IgG (if initially positive) are also recommended.

Useful For: As a serological aid in the diagnosis of thymoma, especially in patients with onset of myasthenia gravis (MG) younger than 45 years. As a screening test for MG in older patients, especially when tests for muscle AChR antibodies are negative. Serial measurements are useful in monitoring the efficacy of immunosuppressant treatment in patients with MG. Serial measurements are useful after treatment of thymoma. Serial measurements in recipients of D-penicillamine or bone marrow allografts may be useful in monitoring autoimmune complications and graft-versus-host disease, respectively.

Interpretation: Striational antibodies occur in approximately: -14% of patients with thymoma without clinical evidence of MG - 30% of patients with acquired (autoimmune) myasthenia gravis (MG) - 74% of patients with thymoma in association with MG - 25% of rheumatoid arthritis (RA) patients treated with D-penicillamine - 4% in untreated RA patients - 5% of patients with Lambert-Eaton myasthenic syndrome (LES) and/or small-cell lung carcinoma (SCLC) [MGLES / Myasthenia Gravis [MG]/Lambert-Eaton Syndrome [LES] Evaluation and PAVAL / Paraneoplastic Autoantibody Evaluation, Serum] - In some bone marrow recipients with graft-versus-host disease. The incidence in healthy subjects is < 1%. A rising titer after removal of thymoma may be indicative of tumor recurrence.

Reference Values:
<1:120

Strict Criteria Sperm Morphology for Infertility Diagnosis and Treatment, Semen

Clinical Information: Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Abnormalities in sperm morphology are related to: defects in sperm transport, sperm capacitation, the acrosome reaction, binding/penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple’s IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).

Useful For: Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

Interpretation: Categorizing sperm according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

Reference Values:
Normal forms
> or =4.5%
Germinal cells/mL
<4 x 10(6) (normal)
> or =4 x 10(6) (Elevated germinal cells in semen are of unknown clinical significance)
WBC/mL
<1 x 10(6) (normal)
> or =1 x 10(6) (Elevated white blood cells in semen are of questionable clinical significance)

sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

**Reference Values:**
- **Normal forms:** \( > \text{or} = 4.5\% \)
- **Germinal cells/mL**
  - \(< 4 \times 10^{6}\) (normal)
  - \( > \text{or} = 4 \times 10^{6}\) (elevated germinal cells in semen are of unknown clinical significance)
- **WBC/mL**
  - \(< 1 \times 10^{6}\) (normal)
  - \( > \text{or} = 1 \times 10^{6}\) (elevated white blood cells in semen are of questionable clinical significance)

**Clinical References:**
1. Kruger Morphology Conference, Boston, MA, October 9, 1993

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**STRNG 63866**

**Strongyloides Antibody, IgG, Serum**

**Clinical Information:** Strongyloidiasis is caused by Strongyloides stercoralis, a nematode endemic to tropical and subtropical regions worldwide. Strongyloides stercoralis is also prominent in the southeastern United States, including in rural areas of Kentucky, Tennessee, Virginia, and North Carolina. A small series of epidemiological studies in the United States identified that between 0 to 6.1\% of individuals sampled had antibodies to Strongyloides stercoralis. Strongyloides stercoralis has a complex lifecycle that begins with maturation to the infective filariform larva in warm, moist soil. The larvae subsequently penetrate exposed skin and migrate hematogenously to the lungs, from where they ascend the bronchial tree and are swallowed. Once in the small intestine, filariform larva mature into the adult worms that burrow into the mucosa. Gravid female worms produce eggs that develop into noninfectious rhabditiform larvae in the gastrointestinal tract and are eventually released in the stool. The time from dermal penetration to appearance of Strongyloides in stool samples is approximately 3 to 4 weeks. The most common manifestations of infection are mild and may include epigastric pain, mild diarrhea, nausea, and vomiting. At the site of filariform penetration, skin may be inflamed and itchy- this is referred to as "ground itch." Migration of the larva through the lungs and up the trachea can produce a dry cough, wheezing, and mild hemoptysis. Eosinophilia, though common among patients with strongyloidiasis, is not a universal finding and the absence of eosinophilia cannot be used to rule-out infection. In some patients, particularly those with a depressed immune system, the rhabditiform larvae may mature into the infectious filariform larvae in the gastrointestinal tract and lead to autoinfection. The filariform larvae subsequently penetrate the gastrointestinal mucosa, migrate to the lungs and can complete their lifecycle. Low level autoinfection can maintain the nematode in the host for years to decades. Among patients who become severely immunocompromised, however, autoinfection may lead to hyperinfection and fatal disseminated disease. Hyperinfection has also been associated with underlying human T-cell lymphotropic virus type 1 (HTLV-1) infection. Uncontrolled, the larvae can disseminate to the lungs, heart, liver, and central nervous system. Septicemia and meningitis are common in cases of Strongyloides hyperinfection due to seeding of the bloodstream and central nervous system with bacteria originating from the gastrointestinal tract.

**Useful For:** Screen for the presence of IgG-class antibodies to Strongyloides

**Interpretation:** Positive: IgG antibodies to Strongyloides were detected, suggesting current or past infection. False-positive results may occur with other helminth infections (eg, Trichinella, Taenia solium). Clinical correlation is required. Negative: No detectable levels of IgG antibodies to Strongyloides. Repeat testing in 10 to 14 days if clinically indicated.

**Reference Values:**
- **Negative**

**Clinical References:**
2. Starr MC, Montgomery SP: Soil-transmitted

**STCH**

**Strychnine, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Potentially lethal concentrations are in excess of 500 ng/mL

**FSTYR**

**Styrene, Occupational Exposure, Blood**

**Reference Values:**

Normal (Unexposed population):
None detected

Exposed:

Biological Exposure Index (BEI):
0.55 mg/L (end of shift)

0.02 mg/L (prior to next shift)

Toxic:
Not established

**TELOF**

**Subtelomeric Region Anomalies, FISH**

**Clinical Information:** This test is appropriate for individuals with clinical features including intellectual disability, developmental delay, mental retardation, autism, dysmorphic features, behavior disorders, learning disability, cognitive impairment of unknown etiology or individuals with a family member previously diagnosed with a subtelomere abnormality. Telomere caps of (TTAGGG)n repeats constitute 3 Kb to 20 Kb at the ends of each human chromosome. Centromeric to the telomere caps are 100 Kb to 300 Kb of telomere-associated repeats (TAR). Unique DNA sequences investigated for this test are centromeric to the TAR ending. The telomere-specific DNA probes are derived from the area near the junction of the TARs and unique sequences. Because of high gene concentrations in telomeric regions, there is an intense interest in subtle abnormalities involving the telomeres. For example, subtle abnormalities have been reported involving the telomeres in 7.4% of a large population of children with moderate-to-severe mental retardation. Abnormalities involving the telomere regions also are suspected in individuals with nonspecific dysmorphic features or couples with multiple miscarriages who are karyotypically normal. A standard chromosome analysis must be performed first to rule out microscopically observable karyotypic abnormalities. Microdeletions that are outside of the probe location are undetectable and this test cannot detect DNA molecular alterations such as point mutations.

**Useful For:** Diagnosis of subtelomeric chromosome abnormalities and rearrangements

**Interpretation:** A deletion results in the loss of a p-arm or q-arm specific probe, and a cryptic translocation causes an exchange between the involved chromosome arms. Duplications, derivative chromosomes, and insertions of subtelomeric regions also can be detected. Family studies may be necessary following abnormal results from this FISH study, as parents may carry balanced translocations or deletions that are found in their children.
Reference Values:
An interpretive report will be provided.


**Succinic Dehydrogenase Stain (Bill Only)**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**Succinylacetone, Blood Spot**

Clinical Information: Tyrosinemia type 1 (Tyr 1) is an autosomal recessive condition caused by fumarylacetoacetate hydrolase (FAH) deficiency. Tyr 1 can cause severe liver disease, hypophosphatemic rickets, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life. Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione is available and is particularly effective when initiated in newborns. The incidence of Tyr 1 is approximately 1 in 100,000 live births. While tyrosine can be determined by routine newborn screening, it is not a specific marker for Tyr 1 and often may be associated with common and benign transient tyrosinemia of the newborn. Succinylacetone (SUAC) is a specific marker for Tyr 1, but is not detectable by routine newborn screening. This assay determines SUAC in newborn blood spots by tandem mass spectrometry. Additional follow-up testing may include confirmatory molecular analysis of the FAH gene.

Useful For: Second-tier newborn screening for tyrosinemia type 1 (Tyr 1) in blood spots with nonspecific elevations of tyrosine Diagnosis of Tyr 1 Follow-up of patients with Tyr 1

Interpretation: Normal: <5.0 mcM Elevations of succinylacetone (SUAC) above the reference range are indicative of tyrosinemia type 1 (Tyr 1). Patients with Tyr 1 who are treated with diet and/or 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (nitisinone) should have declining or normal values of SUAC.

Reference Values:
An interpretive report will be provided.


**Succinyladenosine, CSF**

Reference Values:
Reference Range: 0.74 – 4.92 umol/L

**Sugar Cane (Saccharum officinarum) IgE**

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Sulfamethoxazole, Serum**

**Clinical Information:** Sulfamethoxazole is a sulfonamide antibiotic that is administered in conjunction with another antibacterial, trimethoprim. These agents are used to treat a variety of infections including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients such as HIV-positive individuals. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Monitoring of sulfamethoxazole is indicated only when prolonged (>3 months) therapy is required. Sulfamethoxazole is absorbed readily after oral administration, with peak serum concentration occurring 2 to 3 hours after an oral dose. Its average elimination half-life is 6 to 10 hours. Toxicity includes crystalluria with resultant calculi and renal disease. Toxicity is due to a high concentration of acetylated, relatively insoluble forms of the drug. Excess fluid should be taken with sulfamethoxazole to avoid formation of urine sulfonamide crystals.

**Useful For:** Monitoring therapy to ensure drug absorption, clearance, or compliance

**Interpretation:** Serum drug concentrations should be interpreted with respect to the minimum inhibitory concentration (MIC) of targeted organisms. Most patients will display peak steady-state serum concentrations >50 mcg/mL when drawn at least 1 hour after an oral dose. Targets concentrations may be higher, depending on the intent of therapy. For Pneumocystis carinii pneumonia (PCP pneumonia), peak concentrations: 100-150 mcg/mL Toxicity: >200 mcg/mL Toxicity (formation of urinary crystals)
associated with sulfamethoxazole occurs with prolonged exposure to serum concentrations >125 mcg/mL.

**Reference Values:**
>50 mcg/mL

**Clinical References:**

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**Sulfate, 24 Hour, Urine**

**Clinical Information:** Urinary sulfate is a reflection of dietary protein intake, particularly meat, fish, and poultry, which are rich in sulfur-containing amino acids methionine and cysteine. Urinary sulfate can be used to assess dietary protein intake for nutritional purposes. A protein-rich diet has been associated with an increased risk for stone formation, possibly due, in part, to an increase in urinary calcium excretion caused by acid production from metabolism of sulfur-containing amino acids.(1,2) Indeed, urinary sulfate excretion is higher in patients who have kidney stones than in individuals who do not form stones. Thus, urinary sulfate excretion may provide an index for protein-induced calciuria.(1) Sulfate is a major anion in the urine that has significant affinity for cations and modulates the availability of cations for reacting with other anions in the urine. It thus is an important factor of urinary supersaturation(3) for various crystals or stones such as calcium oxalate, hydroxyapatite, and brushite. For example, a high sulfate concentration may modulate the availability of calcium for reacting with oxalate and thus affect the propensity for calcium oxalate stone or crystal formation. Urinary sulfate also has a major impact on buffering or providing hydrogen ions and as such modulates the supersaturation of uric acid.

**Useful For:** Urinary sulfate can be used to assess the nutrition intake of animal protein. It also can be a reflection of protein intake and can be assessed in patients with stone disease as related to stone supersaturation and prevention of stone disease.

**Interpretation:** Urinary sulfate is a reflection of dietary protein intake, particularly of meat, and thus can be used as an index of nutritional protein intake. It also is used in the calculation of urinary supersaturation of various crystals or stones.

**Reference Values:**
7-47 mmol/24 hours

**Clinical References:**

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**Sulfatide Autoantibody Test**

**Clinical Information:** Background information: Peripheral neuropathies (PNs) are a group of neurological disorders affecting one or more of the peripheral nerves (1,2). Causes of PN include nerve compression, genetic mutations, inflammation, metabolic abnormalities, vitamin deficiencies, exposure to...
toxins or drugs, or the presence of autoimmune antibodies (1). Symptoms of PN vary based on location and mechanism of nerve damage but can include sensory impairment, distal weakness, loss of sensation, muscle weakness, and pain (1,2). PNs are typically classified based on the types of nerves affected, predominantly motor, predominantly sensory, or a combination of both (2). IgG and more commonly IgM Antibodies to sulfatide have been associated with sensory and sensory-motor neuropathies sometimes accompanied by pain (3,4,5). Additionally, IgG anti-sulfatide antibodies have been associated with distal sensory polyneuropathy (DSP) in individuals with HIV (6).

**Reference Values:**

**Interpretive Criteria**

Interpretation and Comments provided on each report. They are dependent upon results.

**Reference Range:**

- **anti-Sulfatide IgG:**
  - Negative: < 1:2000
  - Borderline*: 1:2000
  - Positive: >= 1:2000

- **anti-Sulfatide IgM:**
  - Negative: < 1:2000
  - Borderline*: 1:2000
  - Positive: >= 1:2000

*Samples in the borderline range have an elevated level of anti-sulfatide antibodies on the screen assay, but the level of antibodies is below the positive cut off value.

**Clinical References:**


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**FSLFU**

**Sulfonylurea Screen, Urine**

**Reference Values:**

**Reference Range:** Not Established

- Acetohexamide, UR: ug/mL
- Chlorpropamide, UR: ug/mL
- Tolazamide, UR: ug/mL
- Tolbutamide, UR: ug/mL
- Glimepiride, UR: ng/mL
- Glipizide, UR: ng/mL
- Glyburide, UR: ng/mL
- Nateglinide, UR: ng/mL
- Repaglinide, UR: ng/mL

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**FSUNG**

**Sunflower Seed IgG**

**Interpretation:** mcg/mL of IgG

**Lower Limit of Quantitation:** 2.0

**Upper Limit of Quantitation:** 200

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility
of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Sunflower Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Supersaturation Profile, 24 Hour, Urine**

**Clinical Information:** Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate). (1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

**Useful For:** Diagnosis and management of patients with renal lithiasis: -In patients who have a radiopaque stone, for whom stone analysis is not available, the supersaturation data can be used to predict the likely composition of the stone. This may help in designing a treatment program. -Individual components of the supersaturation profile can identify specific risk factors for stones. -During follow-up,
changes in the urine supersaturation can be used to monitor the effectiveness of therapy by confirming that the crystallization potential has indeed decreased. Urine ammonium can be used to evaluate renal excretion of acid and urine pH. The protein catabolic rate, calculated from the urine urea nitrogen, can be used to estimate a patient's protein intake.

**Interpretation:** Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution is negative for undersaturated solutions and positive for supersaturated solutions. In most cases the supersaturation levels are slightly positive even in normal individuals but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of nonstone formers, on average, the DG is even more positive in those individuals who do form kidney stones. The "normal" values were simply derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of nonstone formers. Those DG values that are outside the expected range in a population of nonstone formers are marked "abnormal." If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg, excessive consumption of meat protein). A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption, or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base) this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. The protein catabolic rate is calculated from urine urea. Under routine conditions, the required protein intake is often estimated as 0.8 g/ kg body weight. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load) and a higher urine pH promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): urinary volume, calcium, pH, and citrate significantly influence the supersaturation for calcium phosphate. Of note, a urine pH <6 may help reduce the tendency for these stones to form. -Uric acid stones: urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is >6. -Sodium urate stones: alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones.

**Reference Values:**

SUPERSATURATION REFERENCE MEANS (DG)

- Calcium oxalate: 1.77
- Brushite: 0.21
- Hydroxyapatite: 3.96
- Uric acid: 1.04
- Sodium urate: 1.76

INDIVIDUAL URINE ANALYTES
OSMOLALITY
0-11 months: 50-750 mOsm/kg
≥12 months: 150-1,150 mOsm/kg

pH
4.5-8.0

ALL REFERENCE RANGES BELOW ARE BASED ON 24-HOUR COLLECTIONS.

SODIUM
41-227 mmol/24 h
Reference values have not been established for patients <16 years of age.

POTASSIUM
17-77 mmol/24 h
Reference values have not been established for patients <16 years of age.

CALCIUM
Males: <250 mg/24 h
Females: <200 mg/24 h
Reference values have not been established for patients <18 years and >83 years of age

MAGNESIUM
51-269 mg/24 h
Reference values have not been established for patients <18 years and >83 years of age

CHLORIDE
40-224 mmol/24 h
Reference values have not been established for patients <16 years of age.

PHOSPHORUS
<1,100 mg/24 h

SULFATE
7-47 mmol/24 h

CITRATE EXCRETION
0-19 years: not established
20 years: 150-1,191 mg/24 h
21 years: 157-1,191 mg/24 h
22 years: 164-1,191 mg/24 h
23 years: 171-1,191 mg/24 h
24 years: 178-1,191 mg/24 h
25 years: 186-1,191 mg/24 h
26 years: 193-1,191 mg/24 h
27 years: 200-1,191 mg/24 h
28 years: 207-1,191 mg/24 h
29 years: 214-1,191 mg/24 h
30 years: 221-1,191 mg/24 h
31 years: 228-1,191 mg/24 h
32 years: 235-1,191 mg/24 h
33 years: 242-1,191 mg/24 h
34 years: 250-1,191 mg/24 h
35 years: 257-1,191 mg/24 h
36 years: 264-1,191 mg/24 h
37 years: 271-1,191 mg/24 h
38 years: 278-1,191 mg/24 h
39 years: 285-1,191 mg/24 h

Current as of July 8, 2016 11:28 am CDT
40 years: 292-1,191 mg/24 h
41 years: 299-1,191 mg/24 h
42 years: 306-1,191 mg/24 h
43 years: 314-1,191 mg/24 h
44 years: 321-1,191 mg/24 h
45 years: 328-1,191 mg/24 h
46 years: 335-1,191 mg/24 h
47 years: 342-1,191 mg/24 h
48 years: 349-1,191 mg/24 h
49 years: 356-1,191 mg/24 h
50 years: 363-1,191 mg/24 h
51 years: 370-1,191 mg/24 h
52 years: 378-1,191 mg/24 h
53 years: 385-1,191 mg/24 h
54 years: 392-1,191 mg/24 h
55 years: 399-1,191 mg/24 h
56 years: 406-1,191 mg/24 h
57 years: 413-1,191 mg/24 h
58 years: 420-1,191 mg/24 h
59 years: 427-1,191 mg/24 h
60 years: 434-1,191 mg/24 h
>60 years: not established

**OXALATE**
0.11-0.46 mmol/24 h

**URIC ACID**
Diet-dependent: <750 mg/24 h

**CREATININE**
Normal values mg per 24 hours:
Males: 955-2936 mg/24 hours
Females: 601-1689 mg/24 hours
Reference ranges for male and female patients <18 and >83 years of age have not been established.

The expected urine creatinine excretion per 24 hours:
Males: 13-29 mg/kg of body weight/24 hours
Females: 9-26 mg/kg of body weight/24 hours

Reference ranges for male and female patients <18 and >83 years of age have not been established.
Note: To convert to mg/kg of body weight/24 hours, divide the mg/24 h result by body weight in kg.

**AMMONIUM**
15-56 mg/24 hour
Reference values have not been established for patients <18 years and >77 years of age.

**UREA NITROGEN**
5.0-16.0 mg/24 hour

**PROTEIN CATABOLIC RATE**
56-98 g/kg/24 hour

Supersaturation Profile, Pediatric, Random, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (e.g., citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (e.g., calcium oxalate). Since the supersaturation of urine has been shown to correlate with stone type, therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

Useful For: Diagnosis and management of patients with renal lithiasis: - In patients who have a radiopaque stone, for whom stone analysis is not available, the supersaturation data can be used to predict the likely composition of the stone. This may help in designing a treatment program - Individual components of the supersaturation profile can identify specific risk factors for stones - During follow-up, changes in the urine supersaturation can be used to monitor the effectiveness of therapy by confirming that the crystallization potential has indeed decreased - Urine ammonium can be used to evaluate renal excretion of acid and urine pH.

Interpretation: Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive even in normal individuals but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of nonstone formers, on average, the DG is even more positive in those individuals who do form kidney stones. The "normal" values are simply derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of nonstone formers. Those DG values that are outside the expected range in a population of nonstone formers are marked "abnormal." A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (e.g., diarrhea or malabsorption), or an exogenous acid load (e.g., excessive consumption of meat protein). An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (i.e., primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption, or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load) and a higher urine pH promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: - Calcium oxalate stones: Urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. - Calcium phosphate stones (apatite or brushite): Urinary volume, calcium, pH, and citrate significantly influence the supersaturation for calcium phosphate. Of note, a urine pH < 6 may help reduce the tendency for these stones to form. - Uric acid stones: Urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is > 6. - Sodium urate stones: Alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones. The following reference means for calculated supersaturation apply to 24-hour timed collections. No information is available for random collections. Brushite: 0.21 Hydroxyapatite: 3.96 Uric acid: 1.04
Sodium urate: 1.76 Values for individual analytes that are part of this panel on a random urine collection are best interpreted as a ratio to the creatinine excretion. Following are pediatric reference ranges for the important analytes for which pediatric data is available. Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048 Matos V, Van Melle G, Werner D, et al: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis 1999;34:e1 Uric Acid/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 >1.189 <2.378 0.5-1 >1.040 <2.229 1-2 >0.743 <2.080 2-3 >0.698 <1.932 3-5 >0.594 <1.635 5-7 >0.446 <1.189 7-10 >0.386 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594 Matos V, Van Melle G, Werner D, et al: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis 1999;34:e1 Phosphate/Creatinine (mg/mg) Age (year) 5th Percentile 0-1 >0.34 <5.24 1-2 >0.34 <3.95 2-3 >0.34 <3.13 3-5 >0.33 <2.17 5-7 >0.33 <1.19 7-10 >0.32 <0.97 10-14 >0.22 <0.86 14-17 >0.21 <0.75 Matos V, van Melle G, Boulat O, et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr 1997;131:252-257 Magnesium/Creatinine (mg/g) Age (year) 95th Percentile 0-1 <0.48 1-2 <0.37 2-3 <0.34 3-5 <0.29 5-7 <0.21 7-10 <0.18 10-14 <0.15 14-17 <0.13 Matos V, van Melle G, Boulat O, et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr 1997;131:252-257 Citrate/Creatinine (mg/mg) Age (year) 5-18 <1.311 Srivastava T, Winston MJ, Auron A, et al: Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res 2009;66:85-90

Reference Values:

**pH:** 4.5-8.0

**OSMOLALITY:**

0-11 months: 50-750 mOsm/kg

> or =12 months: 150-1,150 mOsm/kg

**Ammonium:**

18-77 years: 3-65 mmol/L

No reference values established for <18 years and >77 years of age

**Calcium:**

Random Calcium/Creatinine Ratio:

18-83 years: <0.20 mg/mg

No reference values established for <18 years and >83 years of age

**Magnesium:**

Random Magnesium/Creatinine Ratio:

18-83 years: < or = 0.035 mg/mg

No reference values established for <18 years and >83 years of age

**Clinical References:**


**Supplemental Newborn Screen, Blood Spot**

**Clinical Information:** Newborn screening as a public health measure was initiated in the early 1960s for the identification of infants affected with phenylketonuria (PKU). Since then, additional genetic and nongenetic conditions were included in state screening programs. The goal of newborn screening is to detect diagnostic markers of the selected disorders in blood spots collected from presymptomatic newborns. Inherited disorders of amino acid, fatty acid, and organic acid metabolism typically manifest during the first 2 years of life as acute metabolic crises and usually result in severe neurologic impairment or death. These metabolic decompensations are usually triggered by intermittent febrile illness, such as common viral infections leading to prolonged fasting and increased energy demands. Early identification of affected newborns allows for early initiation of treatment to avoid mortality, morbidity, and disabilities...
due to these disorders. Tandem mass spectrometry (MS/MS) is a powerful multianalyte screening method, which is ideally suited for population-wide testing. Since the early 1990s, MS/MS has made screening possible for more than 30 genetic disorders affecting the metabolism of amino acids, fatty acids, and organic acids based on the profiling of amino acids and acylcarnitines in blood spots. In Mayo's experience, the combined incidence of the disorders identifiable by MS/MS in a single blood spot analysis is approximately 1 in 1,700 newborns. The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) recommends all programs screen for 32 core disorders (available at http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/). These conditions are considered to fulfill 3 basic principles: -Condition is identifiable at a period of time (24-48 hours after birth) at which it would not ordinarily be clinically detected. -Test with appropriate sensitivity and specificity is available. -Demonstrated benefits of early detection, timely intervention, and efficacious treatment. In acknowledgement of the fact that screening tests do not primarily determine disease status, but measure analytes which in most cases are not specific for a particular disease, the American College of Medical Genetics and Genomics report includes 26 secondary conditions that did not meet all 3 selection criteria but are identified nevertheless because most of them are included in the differential diagnosis of screening results observed in core conditions (see Informative Markers for Supplemental Newborn Screening at Mayo Clinic in Special Instructions). Although these conditions do not meet all 3 selection criteria, the possibility of making the diagnosis early in life not only helps avoid unnecessary diagnostic testing, but is also beneficial to the patient's families because genetic counseling and prenatal diagnosis can be offered for subsequent pregnancies. Supplemental newborn screening by MS/MS as described here does not replace current state screening programs, because MS/MS does not allow primary screening for galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia (CAH), cystic fibrosis, biotinidase, sickle cell disease, Pompe disease, severe combined immune deficiency (SCID), critical congenital heart disease, and congenital hearing loss. The simultaneous MS/MS analysis of amino acids, acylcarnitines, and succinylacetone in dried blood spots can be performed in <3 minutes per specimen, generating metabolite profiles that allow for the biochemical diagnosis of multiple disorders. This is in contrast to conventional screening techniques traditionally based on the principle of 1 separate test for each disorder. The performance of Mayo's supplemental newborn screening program is characterized by a very low false-positive rate of 0.024% and a high positive predictive value of 69%.

**Useful For:** Presymptomatic identification of disorders to allow for early initiation of treatment and consequent improvement in the long-term prognosis of affected patients

**Interpretation:** The quantitative measurements of the various amino acids, acylcarnitines, and succinylacetone support the interpretation of the complete profile but for the most part are not diagnostic by themselves. The interpretation is by pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics. The reports are in text form only, values for the more than 60 analytes and analyte ratios are not provided. A report for a normal screening result is reported as: "In this blood spot sample, the amino acid and acylcarnitine profiles by tandem mass spectrometry showed no biochemical evidence indicative of an underlying metabolic disorder." A report for an abnormal screening result includes a quantitative result of the abnormal metabolites, a detailed interpretation of the results, including an overview of the results significance, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), and a phone number for a contact at Mayo Clinic if the referring physician has additional questions.

**Reference Values:** Not applicable

Surgical Pathology Consultation, Slides or Blocks to Scottsdale

Clinical Information: The Mayo Department of Surgical Pathology is staffed by pathologists whose special interests cover the entirety of surgical pathology. Because of the volume of specimens, ranging from common to rare entities, the depth of experience is great. For many years, the Department of Surgical Pathology has provided consultation service on difficult diagnostic problems. The histologic specimens are usually sent by a referring pathologist to 1 of the surgical pathologists who is an expert in the given area. Because this consultation service may not be widely known, it is being extended through the auspices of Mayo Medical Laboratories. Slides received in Mayo Medical Laboratories are reviewed by a surgical pathologist and, when necessary, sent to the pathologist whose area of special interest encompasses the problem. Emphasis is placed on prompt replies. Of necessity, material can be accepted only from pathologists. If the need for special studies is anticipated, appropriate tissue samplings should be sent. Glutaraldehyde-fixed or, if necessary, formaldehyde-fixed wet tissue can be used for electron microscopy. Paraffin blocks or unstained sections from paraffin blocks can be used for special staining methods. In particular, a wide variety of diagnostically important antigens can be identified by means of immunohistochemical procedures which are performed on paraffin sections. This service of Mayo Medical Laboratories does not preclude sending material directly to a preferred surgical pathologist, if the requesting pathologist is so accustomed.

Reference Values:
This request will be processed as a consultation. Appropriate stain(s) will be performed and charged separately. An interpretation will be provided.

STV1 62507
Susceptibility, Mtb Complex, Broth (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

STVP 83597
Susceptibility, Mtb Complex, PZA (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

STV2 62508
Susceptibility, Mtb Cx, 2nd Line (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

TBPZA 34549
Susceptibility, Mycobacterium tuberculosis Complex, Pyrazinamide

Clinical Information: Primary treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide (PZA). Susceptibility testing of each Mycobacterium tuberculosis complex isolate against these first-line antimycobacterial agents is a key component of patient management. The Clinical and Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent.
to be tested in order to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility test results. Current recommendations indicate that laboratories should use a rapid broth method in order to obtain Mycobacterium tuberculosis complex susceptibility data as quickly as possible to help guide patient management. According to the CLSI, resistance can be confirmed by another method or by another laboratory at the discretion of the testing laboratory. This test uses an FDA-cleared commercial system for rapid broth susceptibility testing of Mycobacterium tuberculosis complex against PZA at 300 mcg/mL. Since the literature indicates that broth testing of PZA can, at times, produce falsely resistant results, resistance to PZA by the broth method is automatically confirmed by pncA DNA sequencing. The pncA gene of Mycobacterium tuberculosis complex is responsible for activation of the prodrug PZA and hence PZA activity. Mutations in the pncA gene and upstream promoter region have been reported to account for the majority (70%-97%) of PZA-resistant isolates. However, 3% to 30% of PZA-resistant isolates do not have a corresponding pncA mutation and other genes (eg, rpsA) may also play a role. A separate test is available for testing of the other first-line agents (isoniazid, rifampin and ethambutol).

**Useful For:** Susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture against pyrazinamide Confirming Mycobacterium tuberculosis complex resistance to pyrazinamide

**Interpretation:** Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to pyrazinamide at the critical concentration.

**Reference Values:**
Results are reported as susceptible or resistant.

**Clinical References:**
to second-line antimicrobial agents

**Interpretation:** Results are reported as minimal inhibitory concentrations (MIC) in mcg/mL and tentative interpretations of susceptible or resistant are provided. Agent MIC Range Tested (mcg/mL) MIC Tentative Interpretations (mcg/mL)(1) Susceptible Resistant Amikacin 0.12-16 < or =4.0 >4.0 Cycloserine 2-256 < or =32.0 >32.0 Ethionamide 0.3-40 < or =5.0 >5.0 Kanamycin 0.6-40 < or =5.0 >5.0 Moxifloxacin 0.06-8 < or =2.0 >2.0 Ofloxacin 0.25-32 < or =2.0 >2.0 Para-aminosalicylic acid 0.5-64 < or =2.0 >2.0 Rifabutin 0.12-16 < or =0.5 >0.5 Streptomycin 0.25-32 < or =2.0 >2.0 Isoniazid* 0.03-4 < or =0.25 >0.25 Ethambutol* 0.5-32 < or =4 >4 Rifampin* 0.12-16 < or =1 >1 1. Laboratory-derived tentative interpretations based on MIC breakpoints established relative to the indirect agar proportion method; consensus breakpoint interpretations are not available at this time. (Hall L, Jude KP, Clark SL, et al: Evaluation of the Sensititre MycoTB plate for susceptibility testing of the Mycobacterium tuberculosis complex against first- and second-line agents. J Clin Microbiol 2012;50:3732-3734) *This test is used as an alternative to TB1LN / Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line when reagents are not available to perform the TB1LN test.

**Reference Values:** Results are reported as minimal inhibitory concentration (MIC) values with units of mcg/mL and tentative interpretations of susceptible or resistant are provided.

**Clinical References:**

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**Sweet Gum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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</thead>
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<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
</tbody>
</table>

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*Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1835*
**Sweet Potato, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
</tbody>
</table>
| 6             | > or =100 Strongly positive Reference values apply to all ages.

**Sweet Vernal Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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<td>6</td>
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<td>Strongly positive</td>
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**Reference values apply to all ages.**


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**Swordfish, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
</table>


**SS18F**

**Synovial Sarcoma (SS), 18q11.2 (SS18 or SYT) Rearrangement, FISH, Tissue**

**Clinical Information:** Synovial sarcoma (SS) is a malignant soft tissue tumor that predominantly occurs in the lower limbs of children and young adults. This tumor accounts for approximately 5% to 10% of soft tissue tumors, has a poor prognosis, and may occur in other areas of the body such as the head and neck, heart, abdominal wall, mediastinum, and lung, in addition to the extremities. Histologically, SS is grouped either into the monophasic subtype consisting of mostly spindle cells or the biphasic subtype consisting of epithelial and spindle cells. Depending on the site of origin, the differential diagnosis of SS can include mesothelioma, fibrosarcoma, solitary fibrous tumor, leiomyosarcoma, malignant peripheral nerve sheath tumors, epithelioid sarcoma, and clear cell sarcoma. In addition, when the SS is poorly differentiated, the differential diagnosis broadens to include the small round-blue cell tumors (Ewing sarcoma, alveolar rhabdomyosarcoma, and neuroblastoma). Accurate diagnosis of SS is important for appropriate clinical management of patients. Although immunohistochemical markers can be helpful in the correct diagnosis of these various tumor types, recent molecular studies have shown the superior specificity of molecular makers in differentiating SS from other tumors. A recurrent, tumor-specific translocation t(X;18)(p11.2;q11.2) is observed in approximately 90% of synovial sarcomas. A single gene, SS18 (SYT), has been implicated on 18q11.2, while 1 of 3 related genes, SSX1, SSX2, or infrequently SSX4, is usually involved on Xp11.2. The prevalence of SS18-SSX1 is about twice that of SS18-SSX2 in most studies. Detection of these transcripts is usually performed by reverse transcriptase-PCR (RT-PCR) (SYT / Synovial Sarcoma RT-PCR), which allows specific identification of SS18-SSX1 or SS18-SSX2. Identification of the SS18-SSX1 fusion is associated with an unfavorable outcome with significantly shorter overall survival when compared to the SS18-SSX2 fusion. Unfortunately, RT-PCR results may be equivocal or falsely negative due to many reasons such as when the available RNA is of poor quality or if a rare translocation partner is present. In these cases, FISH...
testing can be used to identify SS18 gene rearrangements in these tumors, which supports the diagnosis of SS.

**Useful For:** Supporting the diagnosis of synovial sarcoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the SYT FISH probe. A positive result suggests rearrangement of the SYT gene region at 18q11.2 and supports the diagnosis of synovial sarcoma (SS). A negative result suggests no rearrangement of the SYT gene region at 18q11.2. However, this result does not exclude the diagnosis of SS.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**SYT 35332**

**Synovial Sarcoma by Reverse Transcriptase PCR (RT-PCR)**

**Clinical Information:** Synovial sarcomas account for 9% to 10% of soft tissue tumors. These tumors occur in 2 major forms: biphasic and monophasic. Monophasic tumors are composed entirely of spindle cells, while biphasic tumors have epithelial cells arranged in glandular structures and mixed with spindle cells. The tumors are usually positive for keratin and epithelial membrane antigen as well as vimentin by immunostaining. Synovial sarcoma is a member of the small round-cell tumor group that includes rhabdomyosarcoma, lymphoma, Wilms tumor, Ewing sarcoma, and desmoplastic small round-cell tumor. While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small round-cell tumor group by light microscopic examination alone can be very difficult, especially true when only small-needle biopsy specimens are available for examination. The use of immunohistochemical stains (eg, keratin and epithelial membrane antigen [EMA]) can assist in establishing the correct diagnosis, but these markers are not entirely specific for synovial sarcoma. Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas and are useful in the diagnosis of these lesions.(1-4) Cytogenetic studies have shown a distinctive chromosomal translocation, t(X;18)(p11;q11), in more than 90% of synovial sarcomas. Cloning of the translocation breakpoint showed that t(X;18) results in the fusion of 2 genes designated as SS18 (at 18q11) and SSX (at Xp11). Two closely related genes, SSX1 and SSX2, have 81% homology in proteins. SS18-SSX1 is present in 55% of cases, while SS18-SSX2 is present in 35% of cases. Patients with SS18-SSX2 translocation usually have greater metastasis-free survival than those with SS18-SSX1. These fusion transcripts can be detected by reverse transcriptase PCR (RT-PCR), by FISH, chromogenic in situ hybridization (CISH), or by classical cytogenetic analyses. The RT-PCR and FISH procedures are the most sensitive methods to detect these fusion transcripts.(3)

**Useful For:** Supporting a diagnosis of synovial sarcoma

**Interpretation:** A positive SS18-SSX1 or SS18-SSX2 result is consistent with a diagnosis of synovial sarcoma. Sarcomas other than synovial sarcoma, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of synovial sarcoma.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
SSX2 encoding proteins with homology to the Kruppel-associated box in human synovial sarcoma.
and SSX, involved in the t(X;18)(p11.2;q11.2) translocation found in human synovial sarcoma. Nat Genet
paraffin-embedded tissue sections of soft tissue sarcomas after laser capture microdissection and RT-PCR.

### Synthetic Cannabinoid Metabolites Screen - Expanded, Urine

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Units</th>
<th>Reporting Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-018 N-pentanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
<td>0.20 Synonym(s): 5-(3-(1-naphthoyl)-1H-indol-1-yl)-pentanoic acid</td>
</tr>
<tr>
<td>JWH-073-N-Butanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
<td>0.20 Synonym(s): 4-(3-(1-naphthoyl)-1H-indol-1-yl)-butanoic acid</td>
</tr>
<tr>
<td>UR-144 N-pentanoic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>0.50 Synonym(s): XLR11 N-pentanoic acid metabolite; 5-(3-(2,2,3,3-tetramethylcyclopropanecarbonyl)-1H-indol-1-yl)pentanoic acid</td>
</tr>
<tr>
<td>AKB48 N-pentanoic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>0.50 Synonym(s): 3-[(tricyclo[3.3.1.13,7]dec-1-ylamino)carbonyl]carboxamide-1H-indazole-1-pentanoic acid; APINACA N-pentanoic acid metabolite</td>
</tr>
<tr>
<td>AB-FUBINACA N-pentanoic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>2.5 Synonym(s): AB-FUBINACA M2; 4-amino-3-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-2-methyl-4-oxobutanoic acid</td>
</tr>
<tr>
<td>AB-CHMINACA 3-methyl-butanolic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>2.5 Synonym(s): N-[1-[(cyclohexylcarbonyl)-L-valine]; AB-CHMINACA M2</td>
</tr>
<tr>
<td>PB-22 3-Carboxyindole</td>
<td>None Detected</td>
<td>ng/mL</td>
<td>5.0 Synonym(s): 1-pentyl-1H-indole-3-carboxylic acid</td>
</tr>
<tr>
<td>5-Fluro-PB-22 3-Carboxyindole</td>
<td>None Detected</td>
<td>ng/mL</td>
<td>5.0 Synonym(s): 1-(5-fluoropentyl)-1H-indole-3-carboxylic acid</td>
</tr>
<tr>
<td>BB-22 3-Carboxyindole</td>
<td>None Detected</td>
<td>ng/mL</td>
<td>5.0 Synonym(s): 1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid</td>
</tr>
<tr>
<td>ADB-PINACA N-pentanoic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>5.0 Synonym(s): 5-(3-((1-amino-3,3-dimethyl-1-oxobutan-2-yl)carbamoyl)-1H-indazol-1-yl)pentanoic acid</td>
</tr>
<tr>
<td>AB-PINACA N-pentanoic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>5.0 Synonym(s): 5-(3-((1-amino-3-methyl-1-oxobutan-2-yl)carbamoyl)-1H-indazol-1-yl)pentanoic acid</td>
</tr>
<tr>
<td>ADBICA N-pentanoic acid</td>
<td>Detected</td>
<td>ng/mL</td>
<td>5.0 Synonym(s): 5-(3-((1-amino-3,3-dimethyl-1-oxobutan-2-yl)carbamoyl)-1H-indazol-1-yl)pentanoic acid</td>
</tr>
</tbody>
</table>

**Test Performed by:** NMS Labs 3701 Welsh Road P.O. Box 433A Willow Grove, PA 19090-0437

### Synthetic Glucocorticoid Screen, Serum

**Clinical Information:** Synthetic glucocorticoids are widely used and have important clinical utility both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these...
steroids may present with clinical features of Cushing syndrome, but with suppressed cortisol levels and
evidence of hypothalamus-pituitary-adrenal axis suppression. This assay does not detect fluticasone
propionate.

**Useful For:** Confirming the presence of listed synthetic glucocorticoids (see Interpretation) Confirming
the cause of secondary adrenal insufficiency

**Interpretation:** This test screens for and quantitates, if present, the following synthetic
glucocorticoids: betamethasone, budesonide, dexamethasone, fludrocortisone, flunisolide,
fluorometholone, megestrol acetate, methylprednisolone, prednisolone, prednisone, triamcinolone, and
triamcinolone acetonide. The presence of synthetic glucocorticoids in serum indicates current or recent
use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by
1 or more orders of magnitude, even trace levels may be associated with Cushingoid features.

**Reference Values:**

**Negative**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cutoff Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.20 mcg/dL</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Fluorometholone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0.30 mcg/dL</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>0.10 mcg/dL</td>
</tr>
</tbody>
</table>

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff
concentration (detection limit).

**Clinical References:**


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**Synthetic Glucocorticoid Screen, Urine**

**Clinical Information:** Synthetic glucocorticoids are widely used and have important clinical utility
both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as
their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these
steroids may present with clinical features of Cushing syndrome, but with suppressed cortisol levels and
evidence of hypothalamus-pituitary-adrenal axis suppression. The fluticasone propionate analyte is
reported with this test and is also available separately, see 17BFP / Fluticasone 17-Beta-Carboxylic Acid,
Urine for more information.

**Useful For:** Confirming the presence of the listed synthetic glucocorticoids (see Interpretation)
Confirming the cause of secondary adrenal insufficiency

**Interpretation:** This test screens for and quantitates, if present, the following synthetic
glucocorticoids: beclomethasone dipropionate, betamethasone, budesonide, dexamethasone,
fludrocortisone, flunisolide, fluorometholone, megestrol acetate, methylprednisolone, prednisolone,
prednisone, triamcinolone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in urine indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with Cushingoid features.

**Reference Values:**

**Negative**

Cutoff concentrations

- Beclomethasone dipropionate: 0.10 mcg/dL
- Betamethasone: 0.10 mcg/dL
- Budesonide: 0.20 mcg/dL
- Dexamethasone: 0.10 mcg/dL
- Fludrocortisone: 0.10 mcg/dL
- Flunisolide: 0.10 mcg/dL
- Fluorometholone: 0.10 mcg/dL
- Megestrol acetate: 0.10 mcg/dL
- Methylprednisolone: 0.10 mcg/dL
- Prednisolone: 0.10 mcg/dL
- Prednisone: 0.10 mcg/dL
- Triamcinolone: 0.30 mcg/dL
- Triamcinolone acetonide: 0.10 mcg/dL

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).

**Clinical References:**


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**TPPA**

**61480**

**Syphilis Antibody by TP-PA, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that Treponema pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Syphilis is categorized by an early primary infection in which patients may have non-specific symptoms, and potentially, genital lesion(s). Patients tested by serology during the primary phase may be negative for antibodies, especially if testing is performed during the first 1 to 2 weeks after symptom onset. As the disease progresses into the secondary phase, antibodies to Treponema pallidum reach peak titers, and may persist indefinitely regardless of the disease state or prior therapy. Therefore, detection of antibodies to nontreponemal antigens, such as cardiolipin (a lipoidal antigen released by host cells damaged by Treponema pallidum) may help to differentiate between active and past syphilis infection. Nontreponemal antibodies are detected by the rapid plasma reagin (RPR) assay, which is typically positive during current infection and negative following treatment or during late/latent forms of syphilis. For prenatal syphilis screening, the syphilis IgG test (SYPGN / Syphilis Antibody, IgG, Serum) is recommended. Testing for IgM-class antibodies to Treponema pallidum should not be performed during routine pregnancy screening unless clinically indicated. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the RPR or the venereal disease research laboratory (VDRL) tests. Because these tests measure the host’s antibody response to nontreponemal antigens, they may lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or the Treponema pallidum particle agglutination (TP-PA). Although the FTA-ABS and TP-PA are technically simple to perform,
they are labor intensive and require subjective interpretation by testing personnel. Due to the low prevalence of syphilis in the United States, the increased specificity of treponemal assays, and the objective interpretation of automated treponemal EIA and multiplex flow immunoassays (MFI), many large clinical laboratories have switched to screening for syphilis using a reverse algorithm. Per this algorithm, serum samples are first tested by an automated treponemal assay (e.g., EIA or MFI). Specimens testing positive by these assays are then reflexed to the RPR assay to provide an indication of the patient's disease state and history of treatment. Recently, the Centers for Disease Control and Prevention recommended that specimens testing positive by a screening treponemal assay and negative by RPR be tested by a second treponemal test (e.g., TP-PA). The results of TP-PA assist in determining whether the results of a screening treponemal test are truly or falsely positive.

**Useful For:** An aid to resolve discrepant results between screening treponemal (e.g., EIA, multiplex flow immunoassay) and nontreponemal (e.g., rapid plasma regain) assays

**Interpretation:** Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for Treponema pallidum specific IgG antibodies using an automated multiplex flow immunoassay (MFI). IgG antibodies to syphilis can remain elevated despite appropriate antimicrobial treatment and a reactive result does not distinguish between recent or past infection. To further evaluate disease and treatment status, samples that are reactive by the syphilis IgG screening test are reflexed to the rapid plasma reagin (RPR) assay, which detects antibodies to cardiolipin, a lipoidal antigen released from host cells damaged by Treponema pallidum. Unlike treponemal-specific antibodies, RPR titers decrease and usually become undetectable following appropriate treatment and can be used to monitor response to therapy. In some patients, the results of the treponemal screening test (syphilis IgG) and RPR may be discordant (e.g., syphilis IgG positive and RPR negative). To discriminate between a falsely-reactive screening result and past syphilis, the Centers for Disease Control and Prevention recommends performing a second treponemal-specific antibody test using a method that is different from the initial screening test (e.g., Treponema pallidum particle agglutination; TP-PA).

(2) In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios (Table 1). In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely-reactive syphilis IgG screen (Table 1). If syphilis remains clinically suspected, a second specimen should be submitted, order SYPHA / Syphilis Antibody Cascade, Serum. Table 1. Interpretation and follow-up of reverse screening results Patient history Test and result Interpretation Follow-up EIA/CIA/MFI RPR TP-PA Unknown history of syphilis Non-reactive N/A N/A No serologic evidence of syphilis None, unless clinically indicated (e.g., early syphilis) Unknown history of syphilis Reactive Reactive N/A Possible syphilis (e.g., early or latent), if previously treated syphilis Historical and clinical evaluation required Known history of syphilis Reactive Non-reactive Reactiveor N/A Past, successfully treated syphilis None CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; MFI, multiplex flow immunoassay; N/A, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination.


**Reference Values:**

Negative

Syphilis Antibody, IgG, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that Treponema pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the venereal disease research laboratory (VDRL) tests. Because these tests measure the host's antibody response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. Recently, EIA and multiplex flow immunoassays (MFI) were introduced to assess serologic response to Treponema pallidum. The Bio-Rad BioPlex Syphilis IgG assay is an example of MFI technology, which utilizes specific, treponemal antigens coated on microspheres for the detection of IgG-class antibodies to Treponema pallidum. The BioPlex Syphilis IgG assay is highly sensitive and specific (see Supportive Data), and allows for an objective interpretation of results. Due to several factors including the low prevalence of syphilis in the United States, the increased specificity of treponemal assays, and the objective interpretation of MFI and EIA technology, initial serologic testing by a treponemal-specific assay (eg, EIA or MFI) is now commonly performed in clinical laboratories. Specimens testing positive by the treponemal-specific assay are then tested by RPR to provide supplementary serologic data, as well as to provide an indication of the patient's disease state and history of treatment. During early primary syphilis, the first antibodies to appear are of the IgM-class, with IgG-class antibodies reaching significant titers later in the primary phase. As the disease progresses into the secondary phase, IgG-class antibodies to Treponema pallidum reach peak titers, and may persist indefinitely regardless of the disease state or prior therapy. For prenatal syphilis screening, the IgG test is recommended. IgM testing should not be performed during routine pregnancy screening unless clinically indicated. Treponema pallidum IgG antibodies persist indefinitely, regardless of the course of the disease. If treatment of an original Treponema pallidum infection was not monitored, a diagnosis of reinfection may actually represent either a resurgence of an inadequately treated earlier infection or persistent IgG antibodies from a resolved infection.

Useful For: An aid in the diagnosis of active Treponema pallidum infection Routine prenatal screening

Interpretation: A positive IgG treponemal test suggests infection with Treponema pallidum at some point in the past, but does not distinguish between treated and untreated infections. This is because treponemal tests (eg, EIA, multiplex flow immunoassay, or fluorescent treponemal antibody-absorbed) may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as rapid plasma reagin, are needed to provide information on a patient's disease state and history of therapy.

Reference Values:
Negative


Syphilis IgG Antibody with Reflex, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that Treponema pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the venereal disease research laboratory (VDRL) tests. Because these tests measure the host's antibody response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1844
fluorescent treponemal antibody-absorbed (FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. Recently, enzyme immunoassays (EIA) and multiplex flow immunoassays (MFI) were introduced to assess serologic response to Treponema pallidum. The Bio-Rad BioPlex Syphilis IgG assay is an example of MFI technology, which utilizes specific, treponemal antigens coated on microspheres for the detection of IgG-class antibodies to Treponema pallidum. The BioPlex Syphilis IgG assay is highly sensitive and specific (see Supportive Data), and allows for an objective interpretation of results. Due to several factors including the low prevalence of syphilis in the United States, the increased specificity of treponemal assays, and the objective interpretation of MFI and EIA technology, initial serologic testing by a treponemal-specific assay (eg, EIA or MFI) is now commonly performed in clinical laboratories. Specimens testing positive by the treponemal-specific assay are then tested by RPR to provide supplementary serologic data, as well as to provide an indication of the patient's disease state and history of treatment. During early primary syphilis, patients may present with nonspecific clinical findings and serology tests may be negative. As the disease progresses into the secondary phase, IgG-class antibodies to Treponema pallidum reach peak titers, and may persist indefinitely regardless of the disease state or prior therapy. For prenatal syphilis screening, the IgG test is recommended. IgM testing should not be performed during routine pregnancy screening unless clinically indicated. Treponema pallidum IgG antibodies persist indefinitely, regardless of whether the patient has been treated or not. To determine if a patient has been treated for syphilis, the RPR test is performed. If the RPR is positive, the results may suggest active, untreated syphilis. In contract, a positive syphilis screening test and a negative RPR most likely suggest past, successfully treated syphilis.

**Useful For:**
- An aid in the diagnosis of active Treponema pallidum infection
- Routine prenatal screening

**Interpretation:**
Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for Treponema pallidum specific IgG antibodies using an automated multiplex flow immunoassay (MFI). A positive IgG treponemal test suggests infection with Treponema pallidum at some point in the past, but does not distinguish between treated and untreated infections. This is because treponemal tests (eg, EIA, MFI, or fluorescent treponemal antibody-absorbed: FTA-ABS) may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as rapid plasma reagin (RPR), are needed to provide information on a patient's disease state and history of therapy. In some patients, the results of the treponemal screening test (syphilis IgG) and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, CDC recommends performing a second treponemal-specific antibody test using a method that is different from the initial screen test (eg, Treponema pallidum particle agglutination: TP-PA).(2) In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table 1. Interpretation and follow-up of reverse screening results: Test and result Patient history EIA/CIA/MFI RPR TP-PA Interpretation Follow-up

| Unknown history of syphilis | Nonreactive | N/A | N/A | No serologic evidence of syphilis | None, unless clinically indicated (eg, early syphilis) | Unknown history of syphilis Reactive Reactive N/A Untreated or recently treated syphilis | See CDC treatment guidelines Unknown history of syphilis Reactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically indicated Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Known history of syphilis Reactive Nonreactive Reactive or N/A Past, successfully treated syphilis None CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; MFI, multiplex flow immunoassay; N/A, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination.


**Reference Values:**
- Negative

**Clinical References:**
1. Tramont EC: Treponema pallidum (Syphilis). In Principles and Practice of
T and B Quantitation, New York

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 co-receptors. B cells can be identified by expression of CD19, while NK cells are typically identified by the co-expression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3), T-helper (CD4), T-suppressor (CD8), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T-lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia(7) recommend changing the diagnostic criteria for CLL from an absolute lymphocyte count >5 x 10⁹/L to a circulating B-cell count >5 x 10⁹/L(8,9) previously defined in the 1996 National Cancer Institute guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

Useful For: Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and...
the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count. (10, 11) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with CD4 count <200 cells/mL.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References:

TCIPF 60590

T- and B-Cell Quantitation and Lymphocyte Proliferation to Antigens and Mitogens Panel

Clinical Information: See individual test IDs.

Useful For: Assessing antigen-specific T-cell responses, global T-cell function, and quantitating lymphocyte subsets in a single orderable test. This panel is most helpful when evaluating patients with immunodeficiencies, where quantitative decreases in T cells can lead to reduced functional antigen and/or mitogen responses. See individual test IDs for additional information.

Interpretation: Since the presence of lymphopenia, particularly in the T-cell compartment, can reduce the magnitude of the proliferative response to both mitogens and antigens, it is helpful to perform simultaneous numerical evaluation of lymphocyte subsets to aid in interpretation of the functional (proliferation) data. See individual test IDs for additional information.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: See individual test IDs.

TCAPF 60589

T- and B-Cell Quantitation and Lymphocyte Proliferation to Antigens Panel

Clinical Information: See individual test IDs.

Useful For: Assessing antigen-specific T-cell responses and quantitating lymphocyte subsets in a single orderable test. This panel is most helpful when evaluating patients with immunodeficiencies, where
quantitative decreases in T cells can lead to reduced functional antigen responses.

**Interpretation:** Since the presence of lymphopenia, particularly in the T-cell compartment, can reduce the magnitude of the proliferative response to antigens, it is helpful to perform simultaneous numerical evaluation of lymphocyte subsets to aid in interpretation of the functional (proliferation) data. See individual test IDs for additional information.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:** See individual test IDs.

### TCMPF 60588 T- and B-Cell Quantitation and Lymphocyte Proliferation to Mitogens Panel

**Clinical Information:** See individual test IDs.

**Useful For:** Assessing global T-cell function and quantitating lymphocyte subsets in a single orderable test. This panel is most helpful when evaluating patients with immunodeficiencies, where quantitative decreases in T cells can lead to reduced functional mitogen responses. See individual test IDs for additional information.

**Interpretation:** Since the presence of lymphopenia, particularly in the T-cell compartment, can reduce the magnitude of the proliferative response to antigens, it is helpful to perform simultaneous numerical evaluation of lymphocyte subsets to aid in interpretation of the functional (proliferation) data. See individual test IDs for additional information.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:** See individual test IDs.

### TBBS 9336 T- and B-Cell Quantitation by Flow Cytometry

**Clinical Information:** Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of one or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression of CD19, while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day.

(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.

(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.

(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening and during summer compared to winter. These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3), T-helper (CD4), T-suppressor (CD8), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4
count is measured for AIDS diagnosis and for initiation of antiretroviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency (SCID) and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of Chronic Lymphocytic Leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia (7) recommends changing the diagnostic criteria for CLL from an absolute lymphocyte count (ALC) >5 x 10^9/L to a circulating B-cell count >5 x 10^9/L (8,9) previously defined in the 1996 National Cancer Institute (NCI) guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

**Useful For:** Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 IWCLL guidelines

**Interpretation:** When the CD4 count falls below 500 cells/mcL, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**
of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients with or without concurrent bone marrow involvement. Specific genetic abnormalities are identified in the majority of cases of T-ALL, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by FISH studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL clone for the prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in T-ALL are listed in the following table.

### Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Cytogenetic change</th>
<th>Genes involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(1p33)</td>
<td>TAL1/STIL</td>
</tr>
<tr>
<td>t(5;14)(q35;q32)</td>
<td>TLX3(HOX11L2)/BCL11B</td>
</tr>
<tr>
<td>t(10;11)(p13;q14)</td>
<td>MLLT10(AF10)/PICALM</td>
</tr>
<tr>
<td></td>
<td>Episomal amplification ABL1</td>
</tr>
<tr>
<td>del(9p)</td>
<td>CDKN2A(p16)</td>
</tr>
<tr>
<td>t(11q23;var)</td>
<td>MLL(t(4;11)(q21;q23) AFF1(AF4)/MLL</td>
</tr>
<tr>
<td>t(10;11)(p13;q23)</td>
<td>MLLT4(AF6)/MLL</td>
</tr>
<tr>
<td>t(9;11)(p22;q23)</td>
<td>MLLT3(AF9)/MLL</td>
</tr>
<tr>
<td>t(10;11)(p13;q23)</td>
<td>MLLT10(AF10)/MLL</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.1)</td>
<td>MLL/ELL</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.3)</td>
<td>MLL/MLLT1(ENL)</td>
</tr>
<tr>
<td>t(7;10)(q34;q24)</td>
<td>MYB/TRA/B</td>
</tr>
<tr>
<td>t(7;10)(q34;q24)</td>
<td>TRB/TLX1(HOX11)</td>
</tr>
<tr>
<td>t(7;11)(q34;p15)</td>
<td>TRB/LMO1(t(7;11)(q34;p13)</td>
</tr>
<tr>
<td>t(14q11.2;var)</td>
<td>TRAD</td>
</tr>
<tr>
<td>t(8;14)(q24.1;q11.2)</td>
<td>MYC/TRA/B(t(10;14)(q24;q11.2)</td>
</tr>
<tr>
<td>t(11;14)(p15;q11.2)</td>
<td>LMO1/TRA/B(t(11;14)(p15;q11.2)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>TP53</td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>(&gt; or =4 abnormalities)</td>
</tr>
</tbody>
</table>

### Useful For:
- Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with T-cell acute lymphoblastic leukemia (T-ALL)
- Identifying and tracking known chromosome abnormalities in patients with T-ALL and tracking response to therapy
- An adjunct to conventional chromosome studies in patients with T-ALL

### Interpretation:
A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

### Reference Values:
An interpretive report will be provided.

### Clinical References:
among the most aggressive of all hematologic and lymphoid neoplasms with the exception of ALCL, which is usually responsive to chemotherapy. There are a few common chromosome abnormalities associated with specific subtypes, which this FISH test can detect: -inv(14)(q11q32) and t(14;14)(q11;q32), which involve the T-cell leukemia/lymphoma 1 gene (TCL1A) and have been associated with T-PLL. -Isochromosome 7q and trisomy 8, which have been associated with hepatosplenic T-cell lymphoma. These probes have diagnostic relevance and can also be used to track response to therapy. This assay detects chromosome abnormalities observed in the blood and bone marrow of patients with T-cell lymphoma (for patients with T-cell acute leukemia, order TALLF / T-Cell Acute Lymphoblastic Leukemia [T-ALL], FISH).

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various T-cell lymphomas. Tracking known chromosome abnormalities and response to therapy in patients with T-cell lymphomas.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone supports a diagnosis of a T-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
T-Cell Receptor Excision Circles (TREC) Analysis, Blood

**Clinical Information:** T cell reconstitution is a critical feature of the recovery of the adaptive immune response and has 2 main components: thymic output of new T cells and peripheral homeostatic expansion of preexisting T cells. It has been shown that though thymic function declines with age, a reasonable output is still maintained into late adult life.(1) In many clinical situations, thymic output is crucial to the maintenance and competence of the T cell effector immune response. Thymic function can be determined by T-cell receptor excision circle (TREC) analysis. TRECs are extrachromosomal DNA byproducts of T-cell receptor (TCR) rearrangement, which are nonreplicative. TRECs are expressed only in T cells of thymic origin and each cell is thought to contain a single copy of TREC. Hence, TREC analysis provides a very specific assessment of T-cell recovery (eg, after hematopoietic cell transplantation) or numerical T-cell competence. There are several TRECs generated during the process of TCR rearrangement and the TCR delta deletion TREC (deltaREC psi-j-alpha signal joint TREC) has been shown to be the most accurate TREC for measuring thymic output.(2) This assay measures this specific TREC using quantitative, real-time PCR. Clinical use of TRECs in HIV and Antiretroviral Therapy: HIV infection leads to a decrease in thymic function. Adult patients treated with highly active antiretroviral therapy (HAART) show a rapid and sustained increase in thymic output.(1) Clinical use of TRECs in Hematopoietic Cell Transplantation (HCT) and Primary Immunodeficiencies (PID): Following HCT, there is a period of prolonged immunodeficiency that varies depending on the nature and type of stem cell graft used and the conditioning regimen, among other factors. This secondary immunodeficiency also includes defects in thymopoiesis.(3-5) It has been shown that numerical T cell recovery is usually achieved by day 100 posttransplant, though there is an inversion of the CD4:CD8 ratio that can persist for up to a year.(4) Also, recovery of T-cell function and diversity can take up to 12 months, although this can be more rapid in pediatric patients. However, recovery of T-cell function is only possible when there is numerical reconstitution of T cells. T cells, along with the other components of adaptive immunity, are key players in the successful response to vaccination post-HCT.(6) Recently, it has been shown in patients who received HCT for severe combined immunodeficiency (SCID) that T cell recovery early after stem cell transplant is crucial to long-term T cell reconstitution.(7) Patients who demonstrated impaired reconstitution were shown to have poor early grafting, as opposed to immune failure caused by accelerated loss of thymic output or long-term graft failure. In this study, the numbers of TRECs early after HCT were most predictive for long-term reconstitution. This data suggests that frequent monitoring of T-cell immunity and TREC numbers after HCT can help identify patients who will fail to reconstitute properly, which would allow additional therapies to be instituted in a timely manner.(7) It would be reasonable to extrapolate such a conclusion to other diseases that are also treated by HCT. TREC Copies and Thymic Output in Adults: Since the adult thymus involutes after puberty and is progressively replaced by fat with age, thymus-dependent T cell recovery has been assumed to be severely limited in adults. However, with TREC analysis it has been shown that the change in thymic function in adults is a quantitative phenomenon rather than a qualitative one and thymic output is not totally eliminated.(1,8,9) Thus, after HCT or HAART, the remaining thymic tissue can be mobilized in adults to replenish depleted immune systems with a potentially broader repertoire of naive T cells. Douek et al have shown that there is a significant contribution by the thymus to immune reconstitution after myeloablative chemotherapy and HCT in adults.(8) In fact, this data shows that there is both a marked increase in the TREC numbers and a significant negative correlation of TREC copies with age posttransplant. In addition to the specific clinical situations elucidated above, TREC analysis can be helpful in identifying patients with primary immunodeficiencies and assessing their numerical T-cell immune competence. It can also be used as a measure of immune competence in patients receiving immunotherapy or cancer vaccines, where maintenance of, T-cell output is integral to the immune response against cancer. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+...
B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day. (10) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. (11-13) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. (11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, (14) and during summer compared to winter. (15) These data, therefore, indicate that timing and consistency in timing of blood collection are critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Measuring T-cell output or reconstitution (thymopoiesis) following hematopoietic cell transplantation or highly active antiretroviral therapy Evaluating thymic function in patients with cellular or combined primary immunodeficiencies, or receiving immunotherapy or cancer vaccines Assessing T-cell recovery following thymus transplants for DiGeorge syndrome

**Interpretation:** T-cell receptor excision circles (TRECs) generally show an inverse correlation with age, though there can be substantial variations in TREC copies relative to T-cell count within a given age group. Following hematopoietic cell transplantation (HCT), highly active antiretroviral therapy (HAART), thymic transplants, etc, TREC typically increases from absent or very low levels (below age-matched reference range) to baseline levels or exceeds baseline levels, showing evidence of thymic rebound, which is consistent with recovery of thymic output and T-cell reconstitution. When a patient is being monitored for thymic recovery posttransplant treatment, this assay recommends that a pretreatment (prior to myeloablative or nonmyeloablative conditioning) or a pretreatment baseline specimen be provided so that appropriate comparisons can be made between the pre- and posttransplant treatment specimens. Since there is substantial variability between individuals in TREC copies, the best comparison is made to the patient's own baseline specimen rather than the reference range (which provides a guideline for TREC copies for age-matched healthy controls). A consultative report will be generated for each patient.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**T-Cell Receptor Gene Rearrangement, PCR, Blood**

**Clinical Information:** The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the "germline" configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions, but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, PCR) and used to determine if a population of T cells shows monoclonal or polyclonal features.

**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population

**Clinical References:**

**T-Cell Receptor Gene Rearrangement, PCR, Bone Marrow**

**Clinical Information:** The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearranged to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the "germline" configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions, but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, PCR) and used to determine if a population of T cells shows monoclonal or polyclonal features.

**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population

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**TCGRV 31140**

**T-Cell Receptor Gene Rearrangement, PCR, Varies**

**Clinical Information:** The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearranged to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the "germline" configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions, but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, PCR) and used to determine if a population of T cells shows monoclonal or polyclonal features.

**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population


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**TCP 89319**

**T-Cell Subsets, Naive, Memory and Activated**

**Clinical Information:** T cells, after completing development and initial differentiation in the thymus, enter the periphery as naive (n) T cells. Naïve T cells undergo further differentiation into effector and memory T cells in the peripheral lymphoid organs after recognizing specific antigenic peptides in the context of major histocompatibility (MHC) molecules, through the antigen-specific T-cell receptor. In addition to the cognate signal of the peptide-MHC complex interaction (the term cognate refers to 2 biological molecules that normally interact), T cells require additional costimulatory signals to complete T-cell activation. Naïve T cells circulate continuously through the lymph nodes and, on recognition of specific antigen, undergo activation. Due to their antigen-inexperienced state, naïve T cells require activation by more potent antigen-presenting cells, such as dendritic cells. Naïve T cells can survive in circulation for prolonged periods of time and are very important in contributing to T-cell repertoire diversity. They proliferate in response to interleukin-2, as a consequence of their response to antigen through recognition of peptide-MHC costimulation. These expanded antigen-specific T cells undergo further differentiation into effector cells. The differentiation of naïve CD8 T cells into cytotoxic effectors...
capable of killing target T cells loaded with exogenous peptides on MHC class I molecules may require additional costimulatory signals from CD4 T cells. Naive CD4 T cells also differentiate into different effector subsets such as Th1, Th2, and Th17, which produce specific cytokines. 

T cells can be subdivided into naive and memory subsets based on the expression of cell-surface markers, such as CD45RA and CD45RO, among others. It was initially thought that the presence of cell-surface CD45RA indicated the naive subset, while the presence of CD45RO indicated memory subsets. But, it has now been shown that multiple, rather than single, markers are required to distinguish these subsets. 

Lanzavecchia and Sallusto proposed a model where naive T cells expressing CD45RA and CCR7 lose CD45RA expression on recognition of antigen. The surface markers for identifying naive T-cell subsets include CD45RA, CD62L (L-selectin), and CD27. Memory T cells are antigen-experienced cells that are present in greater numbers than antigen-specific precursors, and can respond more efficiently and rapidly to specific antigen. Memory T cells can maintain their populations independent of antigen by homeostatic proliferation in response to cytokines. While there are subcategories of memory T cells based on effector function and cell surface and cytolytic molecule expression, the 2 main categories of memory T cells are central memory T cells (Tcm) and effector memory T cells (Tem). Tcm express the CD45RO molecule along with CD62L (L-selectin) and CCR7, and are present mainly in lymphoid tissue. They are able to respond to antigen through rapid proliferation and expansion and differentiation into Tem. By themselves, Tcm are not directly effective in effector cytolytic function. Unlike Tcm, Tem express only CD45RO (not CD62L and CCR7). As the name suggests, Tem have remarkable effector function, though they do not proliferate well. Tem are present throughout the circulation in peripheral tissues providing immune surveillance. Memory T cells are particularly important for maintenance of immune competence since they are associated with a rapid and effective response to pathogens. Therefore, depletion of this compartment has more immediate significance than the depletion of naive T cells. Activation of human T cells is critical for the optimal and appropriate performance of T-cell functions within the adaptive immune response. Activated naive T cells undergo proliferation, as well as subsequent differentiation into effector T cells, and are capable of producing cytokines that can modulate the immune response in a variety of ways. There are several markers associated with T-cell activation, but those most commonly used include CD25 (IL-2R) and MHC class II. Additionally, the expression of the costimulatory molecule CD28 augments the T-cell activation response. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Determining the presence of naive, memory, and activated T cells in various clinical contexts including autoimmune diseases, immunodeficiency states, T-cell recovery posthematopoietic stem cell transplant, DiGeorge syndrome, and as a measure for T-cell immune competence. Naive T-cells can be used as a surrogate marker for thymic-derived T-cell reconstitution, when used in conjunction with assessment of T-cell receptor excision circles (TREC / T-Cell Receptor Excision Circles [TREC] Analysis for Immune Reconstitution) Assessing a patient's relative risk for infections Evaluation of patients with cellular or combined primary immunodeficiencies Evaluation of T-cell reconstitution after hematopoietic stem cell transplant, chemotherapy, biological therapy, immunosuppression or immunomodulator therapy Evaluation of patients with autoimmune diseases Evaluation of HIV-positive patients for naive and memory subsets Evaluation of T-cell immune competence (presence of memory and activated T cells) in patients with recurrent infections.

Interpretation: Absence or reduction of naive T cells with or without T-cell lymphopenia indicates absence or impaired T-cell reconstitution and thymic output. Reduction in activated T cells can also indicate a reduced T-cell immune competent state. Increases in naive T cells with corresponding decreases in the memory T-cell compartment indicates a failure of further differentiation and effector function or selective loss of memory T cells and an increased risk for infection.


**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**TREGS**

**T-Cell Subsets, Regulatory (Tregs)**

**Clinical Information:** Regulatory T cells (Tregs) are a population of CD4+ T cells with a unique role in the immune response. Tregs are crucial in suppressing aberrant pathological immune responses in autoimmune diseases, transplantation, and graft-vs-host disease after allogeneic hematopoietic stem cell transplantation. (1) Tregs are activated through the specific T-cell receptor, but their effector function is nonspecific and they regulate the local inflammatory response through cell-to-cell contact and cytokine secretion. (2) Tregs secrete interleukin (IL)-9 (IL-9), IL-10, and transforming growth factor-beta 1 (TGF-beta 1), which aid in the mediation of immunosuppressive activity. Chief characteristics of the Treg population are surface expression of the CD25 protein (IL-2Ra) and the intracellular presence of the transcription factor Foxp3. The IL-7 receptor (CD127) is downregulated on Foxp3+CD4+CD25+ T cells and provides an excellent alternative cell-surface marker to Foxp3 for detecting natural Tregs (CD4+CD25+CD127lo). (2) Natural Tregs account for 5% to 10% of the total CD4 T-cell population and are derived from thymic precursors. (3) Since CD25 is also expressed on activated T cells, the concomitant use of CD127 permits the differentiation of Tregs from activated T cells. (4) Natural Tregs express the memory marker CD45RO and have limited ability to proliferate. However, within the CD4+CD25+Treg population, there is a subset of Tregs that express the CD45 isoform generally associated with naive T cells (CD45RA), and this subset has been called natural naive (Nn) Tregs. Nn Tregs are most prominent in young adults and decrease with age along with the rest of the naive CD4 T-cell population. (5) Like other naive T cells, Nn Tregs have high proliferative capacity, as well as the suppressor activity of other Treg subsets. Present evidence suggests that Nn Tregs also have a thymic ancestry and are the precursors of the natural Tregs (that are of the memory, antigen-experienced phenotype) and appear to be composed of T cells with self-reactive T-cell receptors. (5) Other subsets of Tregs include the Th3 cells, which secrete high levels of TGF-beta 1 and can be induced by oral administration of antigen, and regulatory T cells...
class 1 (Tr1) cells, which secrete interferon-gamma and IL-10. These Treg subsets are most likely induced in the periphery and are responsible for peripheral tolerance to self antigens. The suppressive activity of Th3 and Tr1 cells is related to the cytokines they produce, TGF-beta 1 and IL-10, respectively. The absence of Tregs as a result of mutations in the FOXP3 gene cause a primary immunodeficiency called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance). Patients with IPEX have a complex manifestation of symptoms including severe watery diarrhea due to significant villous atrophy and lymphocytic infiltration of bowel mucosa, early-onset autoimmune endocrinopathies involving the pancreas or thyroid, and a dermatitic (eczematous) rash. In addition, there are other autoimmune manifestations including autoimmune cytopenias and autoimmune hepatitis. Renal disease is quite common in these patients. Finally, these patients also have a significant predisposition to infections including sepsis, pneumonia, meningitis, and osteomyelitis. Decreased Foxp3+CD4+CD25+Tregs have been reported in 1 patient with a STAT5b mutation. There is an expansion of Nn Tregs in patients with monoclonal gammopathy of undetermined significance and multiple myeloma, likely as a response to the process of malignant transformation. Expansion of Tregs has also been reported in other neoplasias including B-cell chronic lymphocytic leukemia, Hodgkin disease, and solid tumors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Evaluating patients with clinical features of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance) and other primary immunodeficiencies, autoimmune diseases, allergy and asthma, and graft-vs-host disease post-hematopoietic stem cell transplantation

Interpretation: The lack of regulatory T (Treg) cells is associated with mutations in the FOXP3 gene. Low Tregs are also seen in the context of STAT5b mutations. Reduced Nn Tregs and natural Tregs are likely to predispose to autoimmunity, while reductions in Th3/Tr1 cells may impair oral and peripheral tolerance, also facilitating the development of autoimmunity. The presence of expanded naive Tregs may indicate a process of malignant transformation, if other clinical features of malignant disease are present. Increased Tregs in donor stem cell allografts have been associated with a reduced incidence of graft-versus-host disease (ie, mediating a protective effect) after allogeneic stem cell transplantation.

Reference Values:
The appropriate age-related reference values will be provided on the report.

T3 (Triiodothyronine), Free, Serum

Clinical Information: Normally triiodothyronine (T3) circulates tightly bound to thyroxine-binding globulin and albumin. Only 0.3% of the total T3 is unbound (free); the free fraction is the active form. In hyperthyroidism, both thyroxine (tetraiodothyronine; thyroxine: T4) and T3 levels (total and free) are usually elevated, but in a small subset of hyperthyroid patients (T3 toxiciosis) only T3 is elevated. Generally, free T3 (FT3) measurement is not necessary since total T3 will suffice. However, FT3 levels may be required to evaluate clinically euthyroid patients who have an altered distribution of binding proteins (eg, pregnancy, dysalbuminemia). Some investigators recommend the FT3 assay for monitoring thyroid replacement therapy, although its clinical role is not precisely defined.

Useful For: Free triiodothyronine (T3) is a second- or third-level test of thyroid function; it provides further confirmation of hyperthyroidism, supplementing the tetraiodothyronine (T4), sensitive thyrotropin (sTSH), and total T3 assays. Evaluating clinically euthyroid patients who have an altered distribution of binding proteins Monitoring thyroid hormone replacement therapy

Interpretation: Elevated free triiodothyronine (FT3) values are associated with thyrotoxicosis or excess thyroid hormone replacement.

Reference Values:
> or =1 year: 2.0-3.5 pg/mL


T3 (Triiodothyronine), Reverse, Serum

Clinical Information: Reverse triiodothyronine (rT3) differs from triiodothyronine (T3) in the positions of the iodine atoms attached to the aromatic rings. The majority of rT3 found in the circulation is formed by peripheral deiodination (removal of an iodine atom) of T4 (thyroxine). rT3 is believed to be metabolically inactive. The rT3 level tends to follow the T4 level: low in hypothyroidism and high in hyperthyroidism. Additionally, increased levels of rT3 have been observed in starvation, anorexia nervosa, severe trauma and hemorrhagic shock, hepatic dysfunction, postoperative states, severe infection, and in burn patients (ie, "sick euthyroid" syndrome). This appears to be the result of a switchover in deiodination functions with the conversion of T4 to rT3 being favored over the production of T3.

Useful For: An aid in the diagnosis of the "sick euthyroid" syndrome

Interpretation: In hospitalized or sick patients with low triiodothyronine (T3) values, elevated reverse triiodothyronine (rT3) values are consistent with "sick euthyroid" syndrome. Also, the finding on an elevated rT3 level in a critically ill patient helps exclude a diagnosis of hypothyroidism. The rT3 is high in patients on medications such as propylthiouracil, iodopate, propranolol, amiodarone, dexamethasone, and the anesthetic agent halothane. Dilantin decreases rT3 due to the displacement from thyroxine-binding globulin, which causes increased rT3 clearance. To convert from ng/dL to nmol/L, multiply the ng/dL result by 0.01536.
T3 (Triiodothyronine), Total, Serum

Clinical Information: Thyroid hormones regulate a number of developmental, metabolic, and neural activities throughout the body. The thyroid gland synthesizes 2 hormones. The 2 main hormones secreted by the thyroid gland are thyroxine, which contains 4 atoms of iodine (T4), and triiodothyronine (T3). T3 production in the thyroid gland constitutes approximately 20% of the total T3; the rest is generated by the conversion (deiodination) of T4 to T3 by conversion (deiodination) of T4 in peripheral tissues. Circulating levels of T4 are much greater than T3 levels, but T3 is biologically the most metabolically active hormone (3-4 times more potent than T4) although its effect is briefer due to its shorter half-life compared to T4. Thyroid hormones circulate primarily bound to carrier proteins (eg, thyroid-binding globulin: TBG, prealbumin, and albumin); whereas only a small fraction circulates unbound (free). Only the free forms are metabolically active. While both T3 and T4 are bound to TBG, T3 is bound less firmly than T4. Total T3 consists of both the bound and unbound fractions. In hyperthyroidism, both T4 and T3 levels are usually elevated, but in a small subset of hyperthyroid patients only T3 is elevated (T3 toxicosis). In hypothyroidism T4 and T3 levels are decreased. T3 levels are frequently low in sick or hospitalized euthyroid patients. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Second-order testing for hyperthyroidism in patients with low thyroid-stimulating hormone values and normal thyroxine levels Diagnosis of triiodothyronine toxicosis

Interpretation: Triiodothyronine (T3) values >200 ng/dL in adults or > age related cutoffs in children are consistent with hyperthyroidism or increased thyroid hormone-binding proteins. Abnormal levels (high or low) of thyroid hormone-binding proteins (primarily albumin and thyroid-binding globulin) may cause abnormal T3 concentrations in euthyroid patients.

Reference Values:
Adult (> or =20 years): 80-200 ng/dL
Pediatric:
0-5 days: 73-288 ng/dL
6 days-2 months: 80-275 ng/dL
3-11 months: 86-265 ng/dL
1-5 years: 92-248 ng/dL
6-10 years: 93-231 ng/dL
11-19 years: 91-218 ng/dL

serves as a prohormone for T3. Within cells, T4 is either converted to T3, which is about 5 times as potent as T4, or reverse T3, which is biologically inactive. Ultimately, T3, and to a much lesser degree T4, bind to the nuclear thyroid hormone receptor, altering gene expression patterns in a tissue-specific fashion. Under normal physiologic conditions, FT4 and FT3 exert direct and indirect negative feedback on pituitary thyrotropin (thyroid-stimulating hormone: TSH) levels, the major hormone regulating thyroid gland activity. This results in tight regulation of thyroid hormone production and constant levels of FT4 and FT3 independent of the binding protein concentration. Measurement of FT4 and FT3, in conjunction with TSH measurement, therefore represents the best method to determine thyroid function status. It also allows determination of whether hyperthyroidism (increased FT4) or hypothyroidism (low FT4) are primary (the majority of cases, TSH altered in the opposite direction as FT4) or secondary/tertiary (hypothalamic/pituitary origin, TSH altered in the same direction as FT4). By contrast, total T4 and T3 levels can vary widely as a response to changes in binding protein levels, without any change in free thyroid hormone levels and, hence, actual thyroid function status. FT4 is usually measured by automated analog immunoassays. In most instances, this will result in accurate results. However, abnormal types or quantities of binding proteins found in some patients and most often related to other illnesses or drug treatments, may interfere in the accurate measurement of FT4 by analog immunoassays. These problems can be overcome by measuring FT4 by equilibrium dialysis, free from interfering proteins.

**Useful For:** Determining thyroid status of sick, hospitalized patients Used where abnormal binding proteins are known to exist Possibly useful in pediatric patients

**Interpretation:** All free hormone assays should be combined with thyroid-stimulating hormone measurements. Free thyroxine (FT4) <0.8 ng/dL indicates possible hypothyroidism. FT4 >2.0 ng/dL indicates possible hyperthyroidism. Neonates can have significantly higher FT4 levels. The hypothalamic-pituitary-thyroid axis can take several days or, sometimes, weeks to mature.

**Reference Values:**
0.8-2.0 ng/dL
Reference values apply to all ages.

**Clinical References:**

**T4 (Thyroxine), Free, Serum**

**Clinical Information:** Free thyroxine (FT4) comprises a small fraction of total thyroxine. The FT4 is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

**Useful For:** Free thyroxine is measured together with thyroid-stimulating hormone when thyroid function disorders are suspected.

**Interpretation:** Elevated values suggest hyperthyroidism or exogenous thyroxine. Decreased values suggest hypothyroidism. Free thyroxine (FT4) works well to correct total T4 values for thyroxine-binding globulin alterations, but may give misleading values when abnormal binding proteins are present or the patient has other major illnesses (euthyroid sick syndrome).

**Reference Values:**
Adult (> or =20 years): 0.9-1.7 ng/dL
Pediatric:
0-5 days: 0.9-2.5 ng/dL
6 days-2 months: 0.9-2.2 ng/dL
3-11 months: 0.9-2.0 ng/dL
1-5 years: 1.0-1.8 ng/dL
6-10 years: 1.0-1.7 ng/dL
T4 (Thyroxine), Total and Free

**Clinical Information:** THYROXINE (T4), TOTAL: T4 is synthesized in the thyroid gland. T4 is metabolized to T3 peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free or unbound portion. The remainder is bound to thyroxine-binding globulin (TBG), prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted peripherally to triiodothyronine (T3). High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism), and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein binding abnormalities. However, changes in binding proteins can occur which affect the level of total T4 but leave the level of unbound hormone unchanged. THYROXINE (T4), FREE: Free thyroxine comprises a small fraction of total thyroxine. The free T4 (FT4) is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

**Useful For:** Thyroxine (T4) and free T4 are measured together with thyroid-stimulating hormone when thyroid function disorders are suspected.

**Reference Values:**

**T4 (THYROXINE), TOTAL ONLY**

- Adult (> or =20 years): 4.5-11.7 mcg/dL
- Pediatric:
  - 0-5 days: 5.0-18.5 mcg/dL
  - 6 days-2 months: 5.4-17.0 mcg/dL
  - 3-11 months: 5.7-16.0 mcg/dL
  - 1-5 years: 6.0-14.7 mcg/dL
  - 6-10 years: 6.0-13.8 mcg/dL
  - 11-19 years: 5.9-13.2 mcg/dL

**T4 (THYROXINE), FREE**

- Adult (> or =20 years of age): 0.9-1.7 ng/dL
- 0-5 days: 0.9-2.5 ng/dL
- 6 days-2 months: 0.9-2.2 ng/dL
- 3-11 months: 0.9-2.0 ng/dL
- 1-5 years: 1.0-1.8 ng/dL
- 6-10 years: 1.0-1.7 ng/dL
- 11-19 years: 1.0-1.6 ng/dL


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T4 (Thyroxine), Total Only, Serum

**Clinical Information:** Thyroxine (T4) is synthesized in the thyroid gland. T4 is metabolized to triiodothyronine (T3) peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free or unbound portion. The remainder is bound to thyroxine-binding globulin (TBG), prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted...
peripherally to T3. High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism), and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein-binding abnormalities. However, changes in binding proteins can occur that affect the level of total T4 but leave the level of unbound hormone unchanged. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Monitoring treatment with synthetic hormones (synthetic triiodothyronine will cause a low total thyroxine: T4) Monitoring treatment of hyperthyroidism with thiouracil and other antithyroid drugs Total T4 levels offer a good index of thyroid function when the thyroid-binding globulin is normal and nonthyroidal illness is not present

Interpretation: Values >11.7 mcg/dL in adults or > age-related cutoffs in children are seen in hyperthyroidism and patients with acute thyroiditis. Values <4.5 mcg/dL in adults or < age-related cutoffs in children are seen in hypothyroidism, myxedema, cretinism, chronic thyroiditis, and occasionally, subacute thyroiditis. Increased total thyroxine (T4) is seen in pregnancy and patients who are on estrogen medication. These patients have increased total T4 levels (increased thyroxine-binding globulin: TBG levels). Decreased total T4 is seen in patients on treatment with anabolic steroids, or nephrosis (decreased TBG levels). A thyrotropin-releasing hormone stimulation test may be required for certain cases of hyperthyroidism. Clinical findings are necessary to determine if thyroid-stimulating hormone, TBG, or free T4 testing is needed.

Reference Values:
Adult (> or =20 years): 4.5-11.7 mcg/dL
  Pediatric:
  0-5 days: 5.0-18.5 mcg/dL
  6 days-2 months: 5.4-17.0 mcg/dL
  3-11 months: 5.7-16.0 mcg/dL
  1-5 years: 6.0-14.7 mcg/dL
  6-10 years: 6.0-13.8 mcg/dL
  11-19 years: 5.9-13.2 mcg/dL


Tacrolimus, Blood

Clinical Information: Tacrolimus is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by CYP3A4, thus its concentrations are affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range, and adverse effects are common, particularly at high dose and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in stable patients for most solid organ transplants. Trough concentrations should be maintained below 20 ng/mL.

Useful For: Monitoring whole blood tacrolimus concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to tacrolimus with trough whole blood levels of 5.0 to 15.0 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and
comedications. Therapeutic ranges are based on samples drawn at trough (ie, immediately before a
scheduled dose). Blood drawn at other times will yield higher results. The assay is specific for tacrolimus;
it does not cross-react with cyclosporine, cyclosporine metabolites, sirolimus, sirolimus metabolites, or
tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry
are approximately 30% less than by immunoassay.

**Reference Values:**
5.0-15.0 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant
immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be
interpreted in conjunction with this clinical information and any physical signs/symptoms of
rejection/toxicity.

**Clinical References:** 1. Kahan BD, Keown P, Levy GA, et al: Therapeutic drug monitoring of
Drugs 2003;63(12):1247-1297

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**TAPEN 62594**

**Tapentadol and Metabolite, Urine**

**Clinical Information:** Tapentadol, a centrally-acting opioid analgesic, is used in the treatment of
moderate to severe acute and chronic pain and for the management of neuropathic pain associated with
diabetic peripheral neuropathy in adults (extended release formulation only). Tapentadol acts as an opiate
agonist through its binding to mu-opioid receptors and through the inhibition of norepinephrine reuptake.
About 97% of the parent drug is metabolized. The major pathway of tapentadol metabolism is conjugation
with glucuronic acid to produce glucuronides. Tapentadol and its metabolites (N-desmethyltapentadol and
hydroxyl-tapentadol) are excreted almost exclusively via the kidneys and approximately 70% of the drug
is excreted in urine in the conjugated form. The metabolites of tapentadol have no analgesic activity. The
half-life of tapentadol is approximately 4 hours. Opioid analgesics have high abuse potential and the
regular use of tapentadol may result in physical dependence and tolerance. Tapentadol is a schedule II
controlled substance with abuse liability similar to other opioid agonists.

**Useful For:** Monitoring of compliance utilizing tapentadol Detection and confirmation of the illicit use
of tapentadol

**Interpretation:** The presence of tapentadol or N-desmethyltapentadol >50 ng/mL is a strong indicator
that the patient has used tapentadol.

**Reference Values:**
Cutoff: <50 ng/mL

**Clinical References:** 1. Wade WE, Spruill WJ: Tapentadol hydrochloride: a centrally acting oral
(-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCL): a
novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic

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**FIOCA 57944**

**Tapioca IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2
0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“

**Reference Values:**
<0.35 kU/L
**Tarragon, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venoms allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Tay-Sachs Disease, HEXA Gene, Full Gene Analysis**

**Clinical Information:** Tay-Sachs disease (TSD) is an inherited lysosomal storage disease caused by a deficiency of the enzyme beta-hexosaminidase A. It is characterized by accumulation of GM2 gangliosides in cells of the brain and central nervous system. The HEXA gene encodes the alpha subunit of beta-hexosaminidase A and mutations in this gene cause TSD. TSD occurs in approximately 1 in 200,000 live births with a carrier frequency of 1 in 250 to 1 in 300 in the general population. The carrier frequency for this disease in individuals of Ashkenazi Jewish ancestry is 1 in 31. The classic form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. The subacute and adult-onset types of TSD are characterized by later ages of onset and a broad spectrum of disease symptoms and severity. TSD is
inherited in an autosomal recessive manner. Several common mutations in the HEXA gene account for
92% of disease-causing mutations in the Ashkenazi Jewish population. Testing for these mutations is
available as a panel, TSDP / Tay-Sachs Disease, Mutation Analysis, HEXA. In non-Ashkenazi Jewish
individuals, the detection rate for the common mutations is significantly decreased. Sequencing of
the entire HEXA gene detects less common disease-causing mutations. The recommended first-tier test for
TSD carrier screening and diagnosis in all patients is a biochemical test that measures hexosaminidase A
activity in white blood cells, NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes. Refer
to Carrier Testing for Tay-Sachs Disease and Other GM2 Gangliosidosis Variants: Supplementing
Traditional Biochemical Testing with Molecular Methods, Mayo Medical Laboratories Communique
2004 Jul;29(7) for more information regarding testing strategy.

Useful For: Second-tier test for confirming a biochemical diagnosis of Tay-Sachs disease (TSD)
Carrier testing of individuals with a family history of TSD but an affected individual is not available for
testing or disease-causing mutations have not been identified Testing individuals with enzyme activity
consistent with carrier status but negative molecular testing by a panel of common mutations

Interpretation: All detected alterations are evaluated according to American College of Medical
Genetics recommendations.(1) Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Metabolic and Molecular Bases of Inherited Disease. Eighth edition. Edited by CR Scriver, AL Beaudet,
Genetics: ACOG Committee Opinion #318; Screening for Tay-Sachs disease. Obstet Gynecol
2005;106(4):893-894
sequencing is available to evaluate for mutations in all coding regions and exon/intron boundaries of the HEXA gene by ordering HEXZ / Tay-Sachs Disease, HEXA Gene, Full Gene Analysis.

**Useful For:** Carrier testing of individuals of Ashkenazi Jewish ancestry or who have a family history of Tay-Sachs disease. Determining Tay-Sachs disease carrier status for individuals with enzyme activity within the carrier or equivocal ranges. Prenatal diagnosis of Tay-Sachs disease for at-risk families Confirmation of suspected clinical diagnosis of Tay-Sachs disease in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**TB ATPase Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**TCR V-Beta Repertoire Analysis by Spectratyping, Blood**

**Clinical Information:** The rearrangement of the T-cell receptor (TCR) through somatic recombination of V (variable), D (diversity), J (joining), and C (constant) regions is a defining event in the development and maturation of a T cell. TCR gene rearrangement takes place in the thymus. During the process of rearrangement, DNA byproducts are generated called T-cell receptor excision circles (TRECs) and these are used as markers of T cells that have recently emigrated from the thymus (TREC / T-Cell Receptor Excision Circles (TREC) Analysis, Blood). T cells, as part of the adaptive immune system, recognize foreign antigens when they are displayed on the surface of the body's own cells. T cells recognize these foreign antigens as peptides presented in the context of major histocompatibility complex (MHC) molecules through their T-cell receptors. Each TCR exists as 2 different polypeptide chains (heterodimers) called the TCR alpha chain and TCR beta chain, and these are linked by disulfide bonds. The majority of T cells (approximately 90%) in the body express TCRs with alpha and beta chains. A minority of T cells express other T-cell receptors made of different polypeptide chains, gamma and delta. Each T cell has approximately 30,000 identical antigen receptors on its cell surface. A TCR has only 1 antigen-binding site, in contrast to the B-cell receptor, which has 2, and TCRs are never secreted and always remain on the cell surface. The alpha and beta chains are encoded by different gene loci (alpha and beta TCR gene locus). The beta chain locus rearranges before the alpha chain and a functional beta chain has to be produced in order for the T cell to form a pre-T-cell receptor. The expression of the rearranged beta chain with an alpha chain precursor suppresses additional gene rearrangement at the TCR beta locus. The TCR alpha chain locus rearrangement can proceed even with production of a functional alpha chain until there is positive selection of the particular T cell. However, it is important to note that each T cell has a single functional specificity for its TCR. A key concept in understanding the immune response is that there is enormous diversity in the immune system to enable protection against a huge array of pathogens. Since the germline genome is limited in size, diversity is achieved not only by the process of V(D)J recombination but also by junctional (junctions between V-D and D-J segments) deletion of nucleotides and addition of pseudo-random, nontemplated nucleotides. In particular, the CDR3 (complementarity determining region 3), which is the most critical determinant of antigenic specificity in
T cells (and also B cells) is short (between 66-90 nucleotides, approximately 20-30 amino acids) and amenable to assessment of length by fragment length analysis, which provides a size resolution of up to 1 base pair between different CDR3 regions. It is thought that the CDR3-TCR beta chain repertoire in healthy adults contains somewhere between 3 and 4 million unique sequences.(1) Other reports suggest that the unique TCR repertoire after thymic selection is between 10 to 100 million in humans.(2) There is, however, a bias in TCR selection with overrepresentation of certain TCRs that are widely used in individuals who share the same MHC types and these are called "public TCRs." Public TCRs generally have fewer random nucleotide additions in their sequence. The TCR V beta repertoire varies significantly between individuals and populations because of 7 frequently occurring inactivating polymorphisms in functional gene segments and a large insertion/deletion-related polymorphism encompassing 2 V beta gene segments. With this latter situation, the TCR Vb 6-2/6-3 and TCR Vb 4-3 genes are frequently deleted from all ethnic groups.(3) It has been reported that the total number of functional TCR V beta gene segments expressed by an individual varies from 42 to 47.(4) Deep sequencing technologies are evolving to analyze this large diversity in the adaptive immune receptors,(5,6) however; deep sequencing of the T-cell and B-cell receptor genes is not yet widely available and is expensive. Flow cytometry-based analysis to assess TCR V beta diversity is available; however, the antibodies are limited and therefore the assay is not capable of assessing the entire TCR V beta repertoire. On the other hand, TCR beta chain repertoire analysis by fragment length analysis (spectratyping) using fluorescent primers to measure CDR3 length variability, while unable to provide the extreme high resolution of deep sequencing, can provide a global "snapshot" of T-cell receptor repertoire diversity, which is useful for most clinical applications where this level of assessment is required.(7-14) It is important to note that this method uses PCR to amplify the rearranged variable regions to provide adequate template for sequencing (fragment length analysis), and this can introduce bias due to the more efficient amplification of certain templates compared to others. However, despite this limitation, since this assay is not quantitative, it is still able to provide an assessment of diversity by measuring the CDR3 length in various TCR V beta genes, which are organized into 24 families.

**Useful For:** Assessment of T-cell receptor diversity in various clinical contexts including primary immunodeficiencies, monitoring immune reconstitution posthematopoietic cell transplantation, and temporal assessment of repertoire changes in autoimmune diseases and viral infections

**Interpretation:** An interpretive report will be provided with adult and pediatric reference values for the relative contribution of each family to the total repertoire (% diversity ratio). The interpretation will be based on visual analysis of the spectratype (polyclonal, oligoclonal, or monoclonal) for each family as well as assessment of the number of peaks (numerical value not reported), and diversity ratio (DR) (reported value). Information on the distribution of peaks, eg, Gaussian vs non-Gaussian, will also be included in the report, where appropriate. Internal analytical and quality controls will be assessed to determine the suitability of reporting a patient result. Correlation with the clinical context will be made when possible, based on clinical history provided in the patient information sheet (which should be provided with the patient sample).

**Reference Values:**
References values will be provided in the patient report.

**Clinical References:**
Tea IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Tea, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
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<td>2</td>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>3</td>
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</tr>
<tr>
<td>Level</td>
<td>Strongly positive</td>
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</tr>
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<td></td>
</tr>
<tr>
<td>17.5-49.9</td>
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<tr>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>&gt; or =100</td>
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<td></td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FFTEM**

**Temazepam (Restoril), Serum**

**Reference Values:**

Reference Range: 50 - 1000 ng/mL

**TTBS**

**Testosterone, Total and Bioavailable, Serum**

**Clinical Information:** Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone, with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH), and to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest but progressive decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism consequent to aging alone is rare. Measurement of total testosterone (TTST / Testosterone, Total, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH (LH / Luteinizing Hormone [LH], Serum) and follicle stimulating hormone (FSH) (FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particular if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) are recommended in this situation. While both bioavailable and free testosterone can be used for the same indications, determination of bioavailable testosterone levels may be
superior to free testosterone measurement in most situations.

**Useful For:** Testosterone, Total: -Evaluation of men with symptoms or signs of possible hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, osteoporosis, infertility -Evaluation of boys with delayed or precocious puberty -Monitoring testosterone replacement therapy -Monitoring antiandrogen therapy (eg, used in prostate cancer, precocious puberty, treatment of idiopathic hirsutism, male-to-female transgender disorders) -Evaluation of women with hirsutism, virilization, and oligo-amenorrhea -Evaluation of women with symptoms or signs of possible testosterone deficiency -Evaluation of infants with ambiguous genitalia or virilization -Diagnosis of androgen-secreting tumors Testosterone, Total and Bioavailable -This is the recommended second-level test for suspected increases or decreases in physiologically active testosterone -Assessment of androgen status in cases with suspected or known sex hormone-binding globulin binding abnormalities -Assessment of functional circulating testosterone in early pubertal boys and older men -Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism but normal total testosterone levels -Monitoring of testosterone therapy or antiandrogen therapy in older men and in females

**Interpretation:** Total Testosterone and general interpretation of testosterone abnormalities: In males: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter's syndrome, XX males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal." LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmannâ€™s syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, GNRH analogs, cannabis) Increased testosterone levels: In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further work-up is necessary to determine the cause(s) of precocious puberty. In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). In females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia. Nonclassical (mild) variants may not present in childhood, but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17 OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. -Analogous to males, but at lower levels in prepubertal girls, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms. High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values >200 ng/dL. -Polycystic ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly exceed 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, then levels should be kept within the normal female range at all times. Bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) levels should also be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable (TTBS/80065
Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP/8508 Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. Testosterone, Total and Bioavailable: Usually, bioavailable (and free testosterone) levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa:

- Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult.
- Inherited abnormalities in SHBG binding.
- Liver disease and severe systemic illness.
- In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels.
- In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. These men not only have elevated SHBG levels, but albumin levels may also vary, due to coexisting illnesses.

**Reference Values:**

**TESTOSTERONE, TOTAL**

**Males**

- 0-5 months: 75-400 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-130 ng/dL
- 12-13 years: <7-800 ng/dL
- 14 years: <7-1,200 ng/dL
- 15-16 years: 100-1,200 ng/dL
- 17-18 years: 300-1,200 ng/dL
- > or =19 years: 240-950 ng/dL

**Tanner Stages***

- I (prepubertal): <7-20
- II: 8-66
- III: 26-800
- IV: 85-1,200
- V (young adult): 300-950

**Females**

- 0-5 months: 20-80 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-44 ng/dL
- 12-16 years: <7-75 ng/dL
- 17-18 years: 20-75 ng/dL
- > or =19 years: 8-60 ng/dL

**Tanner Stages***

- I (prepubertal): <7-20
- II: <7-47
- III: 17-75
- IV: 20-75
- V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven
relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

**TESTOSTERONE, BIOAVAILABLE**

**Males**

- ≤19 years: not established
- 20-29 years: 83-257 ng/dL
- 30-39 years: 72-235 ng/dL
- 40-49 years: 61-213 ng/dL
- 50-59 years: 50-190 ng/dL
- 60-69 years: 40-168 ng/dL
- > or =70 years: not established

**Females (non-oophorectomized)**

- ≤19 years: not established
- 20-50 years (on oral estrogen): 0.8-4.0 ng/dL
- 20-50 years (not on oral estrogen): 0.8-10 ng/dL
- >50 years: not established


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**Testosterone, Total and Free, Serum**

**Clinical Information:** Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia); adrenal, testicular, and ovarian tumors; and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone (TTST / Testosterone, Total, Serum) is often sufficient for diagnosis, particularly if it is combined with
measurements of LH and follicle-stimulating hormone (FSH) (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of free testosterone or bioavailable testosterone are recommended in this situation; bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) is the preferred assay.

**Useful For:** This assay is the alternative, second-level test for suspected increases or decreases in physiologically active testosterone (preferred: TTBS / Testosterone, Total and Bioavailable, Serum); indications: -Assessment of androgen status in cases with suspected or known sex hormone-binding globulin-binding abnormalities -Assessment of functional circulating testosterone in early pubertal boys and older men -Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism, but normal total testosterone levels -Monitoring of testosterone therapy or antiandrogen therapy in older men and in females

**Interpretation:** Total testosterone and general interpretation of testosterone abnormalities: Males: Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: - Genetic causes (eg, Klinefelter syndrome, XXY males) - Developmental causes (eg, testicular maldescent) - Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) - Infections (eg, mumps) - Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) - Metabolic disorders (eg, hemochromatosis, liver failure) - Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal." LH/FSH levels; causes include: - Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) - Pituitary or hypothalamic tumors - Hyperprolactinemia of any cause - Malnutrition or excessive exercise - Cranial irradiation - Head trauma - Medical or recreational drugs (eg, estrogens, GNRH analogs, cannabis) Increased testosterone levels: - In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further work-up is necessary to determine the causes of precocious puberty. - In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). Females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: - Congenital adrenal hyperplasia: nonclassical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), often to a greater degree than testosterone. - Prepubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty. - Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values >200 ng/dL. - Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly >200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid over treatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate "idiopathic" female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. Free
testosterone: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding -Liver disease and severe systemic illness -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free (TGRP / Testosterone Total and Free, Serum) testosterone should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels, but albumin levels also may vary due to coexisting illnesses.

Reference Values:

TESTOSTERONE, FREE
Males (adult):
20-25 years: 5.25-20.7 ng/dL
25-30 years: 5.05-19.8 ng/dL
30-35 years: 4.85-19.0 ng/dL
35-40 years: 4.65-18.1 ng/dL
40-45 years: 4.46-17.1 ng/dL
45-50 years: 4.26-16.4 ng/dL
50-55 years: 4.06-15.6 ng/dL
55-60 years: 3.87-14.7 ng/dL
60-65 years: 3.67-13.9 ng/dL
65-70 years: 3.47-13.0 ng/dL
70-75 years: 3.28-12.2 ng/dL
75-80 years: 3.08-11.3 ng/dL
80-85 years: 2.88-10.5 ng/dL
85-90 years: 2.69-9.61 ng/dL
90-95 years: 2.49-8.76 ng/dL
95-100 years: 2.29-7.91 ng/dL

Males (children):
<1 year: Term infants
1-8 years: <0.04-0.11 ng/dL
9 years: <0.04-0.45 ng/dL
10 years: <0.04-1.26 ng/dL
11 years: <0.04-5.52 ng/dL
12 years: <0.04-9.28 ng/dL
13 years: <0.04-12.6 ng/dL
14 years: 0.48-15.3 ng/dL
15 years: 1.62-17.7 ng/dL
16 years: 2.93-19.5 ng/dL
17 years: 4.28-20.9 ng/dL
18 years: 5.40-21.8 ng/dL
19 years: 5.36-21.2 ng/dL

Females (adult):
- 20 - <25 years: 0.06-1.08 ng/dL
- 25 - <30 years: 0.06-1.06 ng/dL
- 30 - <35 years: 0.06-1.03 ng/dL
- 35 - <40 years: 0.06-1.00 ng/dL
- 40 - <45 years: 0.06-0.98 ng/dL
- 45 - <50 years: 0.06-0.95 ng/dL
- 50 - <55 years: 0.06-0.92 ng/dL
- 55 - <60 years: 0.06-0.90 ng/dL
- 60 - <65 years: 0.06-0.87 ng/dL
- 65 - <70 years: 0.06-0.84 ng/dL
- 70 - <75 years: 0.06-0.82 ng/dL
- 75 - <80 years: 0.06-0.79 ng/dL
- 80 - <85 years: 0.06-0.76 ng/dL
- 85 - <90 years: 0.06-0.73 ng/dL
- 90 - <95 years: 0.06-0.71 ng/dL
- 95-100+ years: 0.06-0.68 ng/dL

Females (children):
- <1 year: Term infants
  - 1 to 15 days: 0.06-0.25 ng/dL
  - 16 days to 1 year: Values decrease gradually from newborn (0.06-0.25 ng/dL) to prepubertal levels

  *Citation: J Clin Endocrinol Metab, 36(6):1132-1142, 1973

- 1-4 years: <0.04 ng/dL
- 5 years: <0.04-0.07 ng/dL
- 6 years: <0.04-0.14 ng/dL
- 7 years: <0.04-0.23 ng/dL
- 8 years: <0.04-0.34 ng/dL
- 9 years: <0.04-0.46 ng/dL
- 10 years: <0.04-0.59 ng/dL
- 11 years: <0.04-0.72 ng/dL
- 12 years: <0.04-0.84 ng/dL
- 13 years: <0.04-0.96 ng/dL
- 14 years: <0.04-1.06 ng/dL
- 15-18 years: <0.04-1.09 ng/dL
- 19 years: 0.06-1.08 ng/dL

TESTOSTERONE, TOTAL
Males
- 0-5 months: 75-400 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-130 ng/dL
- 12-13 years: <7-800 ng/dL
- 14 years: <7-1,200 ng/dL
- 15-16 years: 100-1,200 ng/dL
- 17-18 years: 300-1,200 ng/dL
- > or =19 years: 240-950 ng/dL

  Tanner Stages*
  I (prepubertal): <7-20
  II: 8-66
  III: 26-800
  IV: 85-1,200
  V (young adult): 300-950
Females
- 0-5 months: 20-80 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-44 ng/dL
- 12-16 years: <7-75 ng/dL
- 17-18 years: 20-75 ng/dL
- > or =19 years: 8-60 ng/dL

Tanner Stages*
- I (prepubertal): <7-20
- II: <7-47
- III: 17-75
- IV: 20-75
- V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References:

Testosterone, Total, Bioavailable, and Free, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia); adrenal, testicular, and ovarian tumors; and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However,
severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone (TTST / Testosterone, Total, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulation hormone (FSH) (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of free testosterone or bioavailable testosterone are recommended in this situation; bioavailable testosterone (see TTBS / Testosterone, Total and Bioavailable, Serum) is the preferred assay.

**Useful For:** Second- or third-order test for evaluating testosterone status (eg, when abnormalities of sex hormone-binding globulin are present)

**Interpretation:** Total Testosterone and General Interpretation of Testosterone Abnormalities: Males: Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XX males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure)

-Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels; causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition or excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, GNRH analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the causes of precocious puberty -In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). Females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: nonclassical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), often to a greater degree than testosterone. -Prepubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values >200 ng/dL. -Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form part of this syndrome. Total testosterone levels may be normal or mildly elevated and, uncommonly, >200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate "idiopathic" female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical endpoints and the primary treatment end point is the clinical response. Bioavailable and Free Testosterone: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) concentration, which may cause total testosterone concentration to change without...
necessarily influencing the bioavailable or free testosterone concentration, or vice versa. Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. Inherited abnormalities in SHBG binding. Liver disease and severe systemic illness. In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free (TGRP / Testosterone Total and Free, Serum) testosterone should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels, but albumin levels also may vary due to coexisting illnesses.

**Reference Values:**

**TESTOSTERONE, TOTAL**

Males
- 0-5 months: 75-400 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-130 ng/dL
- 12-13 years: <7-800 ng/dL
- 14 years: <7-1,200 ng/dL
- 15-16 years: 100-1,200 ng/dL
- 17-18 years: 300-1,200 ng/dL
- > or =19 years: 240-950 ng/dL

Tanner Stages*
- I (prepubertal): <7-20
- II: 8-66
- III: 26-800
- IV: 85-1,200
- V (young adult): 300-950

Females
- 0-5 months: 20-80 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-44 ng/dL
- 12-16 years: <7-75 ng/dL
- 17-18 years: 20-75 ng/dL
- > or =19 years: 8-60 ng/dL

Tanner Stages*
- I (prepubertal): <7-20
- II: <7-47
- III: 17-75
- IV: 20-75
- V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

**TESTOSTERONE, FREE**

Males (adult):
- 20 - <25 years: 5.25-20.7 ng/dL
25 - <30 years: 5.05-19.8 ng/dL
30 - <35 years: 4.85-19.0 ng/dL
35 - <40 years: 4.65-18.1 ng/dL
40 - <45 years: 4.46-17.1 ng/dL
45 - <50 years: 4.26-16.4 ng/dL
50 - <55 years: 4.06-15.6 ng/dL
55 - <60 years: 3.87-14.7 ng/dL
60 - <65 years: 3.67-13.9 ng/dL
65 - <70 years: 3.47-13.0 ng/dL
70 - <75 years: 3.28-12.2 ng/dL
75 - <80 years: 3.08-11.3 ng/dL
80 - <85 years: 2.88-10.5 ng/dL
85 - <90 years: 2.69-9.61 ng/dL
90 - <95 years: 2.49-8.76 ng/dL
95-100+ years: 2.29-7.91 ng/dL

Males (children):
<1 year: Term infants
1 to 15 days: 0.20-3.10 ng/dL*
16 days to 1 year: Values decrease gradually from newborn (0.20-3.10 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-8 years: <0.04-0.11 ng/dL
9 years: <0.04-0.45 ng/dL
10 years: <0.04-1.26 ng/dL
11 years: <0.04-5.52 ng/dL
12 years: <0.04-9.28 ng/dL
13 years: <0.04-12.6 ng/dL
14 years: 0.48-15.3 ng/dL
15 years: 1.62-17.7 ng/dL
16 years: 2.93-19.5 ng/dL
17 years: 4.28-20.9 ng/dL
18 years: 5.40-21.8 ng/dL
19 years: 5.36-21.2 ng/dL

Females (adult):
20 - <25 years: 0.06-1.08 ng/dL
25 - <30 years: 0.06-1.06 ng/dL
30 - <35 years: 0.06-1.03 ng/dL
35 - <40 years: 0.06-1.00 ng/dL
40 - <45 years: 0.06-0.98 ng/dL
45 - <50 years: 0.06-0.95 ng/dL
50 - <55 years: 0.06-0.92 ng/dL
55 - <60 years: 0.06-0.90 ng/dL
60 - <65 years: 0.06-0.87 ng/dL
65 - <70 years: 0.06-0.84 ng/dL
70 - <75 years: 0.06-0.82 ng/dL
75 - <80 years: 0.06-0.79 ng/dL
80 - <85 years: 0.06-0.76 ng/dL
85 - <90 years: 0.06-0.73 ng/dL
90 - <95 years: 0.06-0.71 ng/dL
95-100+ years: 0.06-0.68 ng/dL

Females (children):
<1 year: Term infants
1 to 15 days: 0.06-0.25 ng/dL*
16 days to 1 year: Values decrease gradually from newborn (0.06-0.25 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-4 years: <0.04 ng/dL
5 years: <0.04-0.07 ng/dL
6 years: <0.04-0.14 ng/dL
7 years: <0.04-0.23 ng/dL
8 years: <0.04-0.34 ng/dL
9 years: <0.04-0.46 ng/dL
10 years: <0.04-0.59 ng/dL
11 years: <0.04-0.72 ng/dL
12 years: <0.04-0.84 ng/dL
13 years: <0.04-0.96 ng/dL
14 years: <0.04-1.06 ng/dL
15-18 years: <0.04-1.09 ng/dL
19 years: 0.06-1.08 ng/dL

TESTOSTERONE, BIOAVAILABLE
Males
< or =19 years: not established
20-29 years: 83-257 ng/dL
30-39 years: 72-235 ng/dL
40-49 years: 61-213 ng/dL
50-59 years: 50-190 ng/dL
60-69 years: 40-168 ng/dL
> or =70 years: not established
Females (non-oophorectomized)
< or =19 years: not established
20-50 years (on oral estrogen): 0.8-4.0 ng/dL
20-50 years (not on oral estrogen): 0.8-10 ng/dL
>50 years: not established


Testosterone, Total, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In males, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in males also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligomenorrhea, or infertility. Mild-to-moderate
testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact cause for mild-to-moderate elevations of testosterone often remains obscure. Common causes of pronounced elevations include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult males, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone is often sufficient for diagnosis, particularly if it is combined with measurements of LH (LH / Luteinizing Hormone [LH], Serum) and follicle stimulating hormone (FSH) (FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone Total and Free, Serum) are recommended in this situation. See Steroid Pathways in Special Instructions.

Useful For: Evaluation of men with symptoms or signs of possible hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, osteoporosis, or infertility Evaluation of boys with delayed or precocious puberty Monitoring testosterone replacement therapy Monitoring antiandrogen therapy (eg, used in prostate cancer, precocious puberty, treatment of idiopathic hirsutism, male-to-female transgender disorders, etc.) Evaluation of women with hirsutism, virilization, and oligoamenorrhea Evaluation of women with symptoms or signs of possible testosterone deficiency Evaluation of infants with ambiguous genitalia or virilization Diagnosis of androgen-secreting tumors

Interpretation: In males: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: - Genetic causes (eg, Klinefelter's syndrome, XX males) - Developmental causes (eg, testicular maldescent) - Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) - Infections (eg, mumps) - Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) - Metabolic disorders (eg, hemochromatosis, liver failure) - Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal" LH/FSH levels. Causes include: - Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann r syndromes, congenital hypopituitarism) - Pituitary or hypothalamic tumors - Hyperprolactinemia of any cause - Malnutrition - Excessive exercise - Cranial irradiation - Head trauma - Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause(s) of precocious puberty. In adult males, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value, typically <50% ng/dL). In females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: - Congenital adrenal hyperplasia, Nonclassical (mild) variants may not present in childhood, but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17 OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. - Analogous to
males, but at lower levels in prepubertal girls, increased levels of testosterone are seen in precocious puberty. - Ovarian or adrenal neoplasms. High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values >200 ng/dL. - Polycystic ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly >200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, then levels should be kept within the normal female range at all times. Bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) levels should also be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. See Steroid Pathways in Special Instructions.

Reference Values:

Males

- 0-5 months: 75-400 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-130 ng/dL
- 12-13 years: <7-800 ng/dL
- 14 years: <7-1,200 ng/dL
- 15-16 years: 100-1,200 ng/dL
- 17-18 years: 300-1,200 ng/dL
- > or =19 years: 240-950 ng/dL

Tanner Stages*

- I (prepubertal): <7-20
- II: 8-66
- III: 26-800
- IV: 85-1,200
- V (young adult): 300-950

Females

- 0-5 months: 20-80 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-44 ng/dL
- 12-16 years: <7-75 ng/dL
- 17-18 years: 20-75 ng/dL
- > or =19 years: 8-60 ng/dL

Tanner Stages*

- I (prepubertal): <7-20
- II: <7-47
- III: 17-75
- IV: 20-75
- V (young adult): 12-60

*Tanner stages are based on the median age of puberty onset for males (11.5 years) and females (10.5 years). There is evidence that puberty may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Tetanus Toxoid IgG Antibody, Serum

Clinical Information: Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin, tetanospasmin. Tetanospasmin attaches to peripheral nerve endings and travels to the central nervous system (CNS) where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospasmin), which stimulates development of anti-tetanus toxoid antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. Two to three weeks following vaccination, a patient's immunological response may be assessed by measuring the total anti-tetanus toxoid IgG antibody level in serum. An absence of antibody formation post-vaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Assessment of an antibody response to the tetanus toxoid vaccine An aid to diagnose immunodeficiency

Interpretation: Results > or =0.01 suggest a vaccine response. A tetanus toxoid booster should strongly be considered for patients with anti-tetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients who have a measurable serum level of 0.01 to 1.0 IU/mL.

Reference Values:
- Vaccinated: Positive (> or =0.01 IU/mL)
- Unvaccinated: Negative (<0.01 IU/mL)

Clinical References:

Tetanus Toxoid, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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Reference values apply to all ages.


### FFTEN 57102

**Tetrahydrobiopterin & Neopterin Profile (BH4, N)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BH4 (nmol/L)</th>
<th>Neop (nmol/L)</th>
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<tr>
<td>Adults</td>
<td>10 â€“ 30</td>
<td>8 â€“ 28</td>
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Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

An important consideration for false positive or false negative results is the improper labeling of the patient sample.

### TGFK1 89460

**TGFBR1 Gene, Known Mutation**

**Clinical Information:** Mutations in the TGFBR1 gene have been implicated in a range of autosomal dominant conditions with a considerable degree of phenotypic overlap. The genetic disease most
commonly associated with TGFBR1 mutations is Loeys-Dietz syndrome (LDS), which is characterized by cerebral, thoracic and abdominal arterial aneurysms and/or dissections, as well as skeletal anomalies (chest abnormalities, scoliosis, joint laxity, arachnodactyly). LDS can also be caused by mutations in the TGFBR2 gene. LDS is divided into LDS type I and LDS type II based on phenotype, then further categorized depending on the causative gene. Both LDS type I and II involve the cardiovascular and skeletal manifestations mentioned above. In addition, LDS type I involves craniofacial manifestations including hypertelorism, bifid uvula/cleft palate, and craniosynostosis. LDS type I caused by a TGFBR1 mutation is known as LDS1A, whereas LDS type I caused by a TGFBR2 mutation is known as LDS1B. LDS type II has cutaneous manifestations including velvety and translucent skin, easy bruising, widened and atrophic scars, and uterine rupture. LDS type II caused by a TGFBR1 mutation is known as LDS2A, whereas LDS type II caused by a TGFBR2 mutation is known as LDS2B. Identical mutations can lead to LDS type I or type II, supporting the belief that both types are part of a clinical continuum. Mutations in the TGFBR1 gene have also been identified in conditions with phenotypic overlap with LDS. Marfan syndrome (MFS) is a systemic connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. MFS is most often associated with mutations in the FBN1 gene; however some individuals who meet or nearly meet the clinical diagnostic criteria for MFS have been shown to have mutations in the TGFBR1 gene. Some individuals with mutations in TGFBR1 present with features similar to those seen in vascular type Ehlers-Danlos syndrome (EDS type IV), such as visceral rupture, easy bruising, wide and atrophic scars, joint laxity, translucent skin, velvety skin, or both. In addition, familial thoracic aortic aneurysm and dissection (FTAAD), which involves cardiovascular manifestations only, has been associated with mutations in TGFBR1. Mutations in TGFBR1 may also be observed in Shprintzen Goldberg syndrome (SGS), which is characterized by craniosynostosis, distinctive craniofacial features, skeletal changes, neurologic abnormalities, mental retardation, and brain anomalies among other features. The TGFBR1 gene, which contains 9 exons and is located on chromosome 9q22, encodes the transforming growth factor beta receptor I (TGF beta R-I). TGF beta R-I is a 53 kilodalton protein that belongs to the serine-threonine kinase family of cell surface receptors. This group of receptors regulates a variety of cellular processes, including proliferation, differentiation, cell cycle arrest, apoptosis, and formation of the extracellular matrix. Receptor activation occurs upon binding of TGF beta to transforming growth factor beta receptor II (TGF beta R-II), which then recruits and phosphorylates TGF beta R-I, propagating the signal to downstream transcription factors. Few genotype-phenotype correlations exist for TGFBR1 mutations; indeed, identical mutations have been reported to cause Marfan-like syndrome in some individuals, LDS in others, and FTAAD in others. Approximately 25% of individuals with LDS have an affected parent; while 75% have a de novo mutation (de novo rate for related phenotypes is not reported). TGFBR1 mutations can manifest with a range of phenotypes and variable ages of onset both between families and amongst affected members of the same family. Thus, TGFBR1-related disorders can be diagnostically challenging. Genetic testing for TGFBR1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of LDS or other TGFBR1-associated genetic diseases allows for proper treatment and management of the disease. Additionally, mutation confirmation can allow for preconception/prenatal and family counseling.

**Useful For:** Genetic testing of individuals at risk for a known TGFBR1 mutation

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Clinical Information: Mutations in the TGFBR1 gene have been implicated in a range of autosomal dominant conditions with a considerable degree of phenotypic overlap. The genetic disease most commonly associated with TGFBR1 mutations is Loeys-Dietz syndrome (LDS), which is characterized by cerebral, thoracic and abdominal arterial aneurysms and/or dissections, as well as skeletal anomalies (chest abnormalities, scoliosis, joint laxity, arachnodactyly). LDS can also be caused by mutations in the TGFBR2 gene. LDS is divided into LDS type I and LDS type II based on phenotype, then further categorized depending on the causative gene. Both LDS type I and II involve the cardiovascular and skeletal manifestations mentioned above. In addition, LDS type I involves craniofacial manifestations including hypertelorism, bifid uvula/cleft palate, and craniosynostosis. LDS type I caused by a TGFBR1 mutation is known as LDS1A, whereas LDS type I caused by a TGFBR2 mutation is known as LDS1B. LDS type II has cutaneous manifestations including velvety and translucent skin, easy bruising, widened and atrophic scars, and uterine rupture. LDS type II caused by a TGFBR1 mutation is known as LDS2A, whereas LDS type II caused by a TGFBR2 mutation is known as LDS2B. Identical mutations can lead to LDS type I or type II, supporting the belief that both types are part of a clinical continuum. Mutations in the TGFBR1 gene have also been identified in conditions with phenotypic overlap with LDS. Marfan syndrome (MFS) is a systemic connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. MFS is most often associated with mutations in the FBN1 gene; however some individuals who meet or nearly meet the clinical diagnostic criteria for MFS have been shown to have mutations in the TGFBR1 gene. Some individuals with mutations in TGFBR1 present with features similar to those seen in vascular type Ehlers-Danlos syndrome (EDS type IV), such as visceral rupture, easy bruising, wide and atrophic scars, joint laxity, translucent skin, velvety skin, or both. In addition, familial thoracic aortic aneurysm and dissection (FTAAD), which involves cardiovascular manifestations only, has been associated with mutations in TGFBR1. Mutations in TGFBR1 may also be observed in Shprintzen Goldberg syndrome (SGS), which is characterized by craniosynostosis, distinctive craniofacial features, skeletal changes, neurologic abnormalities, mental retardation, and brain anomalies among other features. The TGFBR1 gene, which contains 9 exons and is located on chromosome 9q22, encodes the transforming growth factor beta receptor I (TGF beta R-I). TGF beta R-I is a 53 kilodalton protein that belongs to the serine-threonine kinase family of cell surface receptors. This group of receptors regulates a variety of cellular processes, including proliferation, differentiation, cell cycle arrest, apoptosis, and formation of the extracellular matrix. Receptor activation occurs upon binding of TGF beta to transforming growth factor beta receptor II (TGF beta R-II), which then recruits and phosphorylates TGF beta R-I, propagating the signal to downstream transcription factors. Few genotype-phenotype correlations exist for TGFBR1 mutations; indeed, identical mutations have been reported to cause Marfan-like syndrome in some individuals, LDS in others, and FTAAD in others. Approximately 25% of individuals with LDS have an affected parent; while 75% have a de novo mutation (de novo rate for related phenotypes is not reported). TGFBR1 mutations can manifest with a range of phenotypes and variable ages of onset both between families and amongst affected members of the same family. Thus, TGFBR1-related disorders can be diagnostically challenging. Genetic testing for TGFBR1 mutations allows for the confirmation of a suspected genetic disease. Confirmation of LDS or other TGFBR1-associated genetic diseases allows for proper treatment and management of the disease. Additionally, mutation confirmation can allow for preconception/prenatal and family counseling.

Useful For: Aiding in the diagnosis of TGFBR1-associated Loeys-Dietz syndrome, Marfan or Marfan-like syndrome, familial thoracic aortic aneurysm and dissection syndrome, and Shprintzen-Goldberg syndrome

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.


**TGFR2 Gene, Known Mutation**

**Clinical Information:** Mutations in the TGFR2 gene have been implicated in a range of autosomal dominant conditions with considerable phenotypic overlap. The genetic disease most commonly associated with TGFR2 mutations is Loey-Dietz syndrome (LDS), which is characterized by cerebral, thoracic, and abdominal arterial aneurysms and/or dissections, as well as skeletal anomalies (chest abnormalities, scoliosis, joint laxity, arachnodactyly). LDS is divided into LDS type I and LDS type II based on the phenotype, then further categorized depending on the causative gene. Both LDS type I and II involve the cardiovascular and skeletal manifestations mentioned above. In addition, LDS type I involves craniofacial manifestations including hypertelorism, bifid uvula/eleft palate, and craniosynostosis. LDS type I caused by a TGFBR1 mutation is known as LDS1A, whereas LDS type I caused by a TGFBR2 mutation, is known as LDS1B. LDS type II has cutaneous manifestations including velvety and translucent skin, easy bruising, widened and atrophic scars, and uterine rupture. LDS type II caused by a TGFBR1 mutation is known as LDS2A, whereas LDS type II caused by a TGFBR2 mutation is known as LDS2B. Identical mutations can lead to LDS type I or type II, supporting the belief that both types are part of a clinical continuum. Mutations in the TGFR2 gene have also been identified in conditions with phenotypic overlap with LDS. Marfan syndrome (MFS) is a systemic connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. MFS is most often associated with mutations in the FBN1 gene; however some individuals who meet or nearly meet the clinical diagnostic criteria for MFS have been shown to have mutations in TGFR2. Familial thoracic aortic aneurysm and dissection (TAAD), which involves cardiovascular manifestations only, has also been associated with mutations in TGFR2. Shprintzen-Goldberg syndrome, a rare disorder characterized by marfanoid habitus, cardiovascular anomalies, mental retardation, and craniosynostosis, has been associated with a TGFR2 mutation. TGFR2 mutations have also been identified in individuals who phenotypically present with vascular type Ehlers-Danlos syndrome (EDS), but tested negative for COL3A1 mutations (the gene typically associated with vascular EDS). Transforming growth factor beta receptor II (TGFR-II) is a 70 to 80 kDa protein that belongs to the serine-threonine kinase family of cell surface receptors. This group of receptors regulates a variety of cellular processes including proliferation, differentiation, cell cycle arrest, apoptosis, and formation of the extracellular matrix. Receptor activation occurs upon binding of transforming growth factor-beta (TGFβ) to TGFR-II, which then recruits and phosphorylates TGFR-I, propagating the signal to downstream transcription factors. TGFR-II is encoded by the TGFR2 gene, which contains 7 exons plus 2 variant exons and is located on chromosome 3p22. Excluding TGFR2 mutations reported in malignancies, more than 50 pathogenic TGFR2 mutations have been associated with the syndromic features described above. The majority of these are missense mutations, although splice site and nonsense mutations have also been reported. The great majority of pathogenic mutations are located in the intracellular serine/threonine kinase domains. Few genotype-phenotype correlations exist for TGFR2 mutations; indeed, identical mutations have been reported to cause MFS in some individuals and LDS in others. Approximately 25% of individuals with LDS have an affected parent, while 75% have a de novo mutation. TGFR2 mutations can manifest with a range of phenotypes and variable ages of onset both between families and among affected members of the same family. Thus, TGFR2-related disorders can be diagnostically challenging. Genetic testing for TGFR2 mutations allows for the confirmation of a suspected genetic disease. Confirmation of LDS or other TGFR2-associated genetic diseases allows for proper treatment and management of the disease, and preconception/prenatal and family counseling. For example, in LDS, aortic dissection has been observed at aortic dimensions that do not confer risk in MFS caused by FBN1 mutations. Therefore, a more aggressive treatment strategy or earlier surgical intervention might be considered if an individual were found to have a TGFR2 mutation rather than an FBN1 mutation.
Useful For: Genetic testing of individuals at risk for a known TGFBR2 mutation

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

TGF2

Clinical Information: Mutations in the TGFBR2 gene have been implicated in a range of autosomal dominant conditions with considerable phenotypic overlap. The genetic disease most commonly associated with TGFBR2 mutations is Loeys-Dietz syndrome (LDS), which is characterized by cerebral, thoracic, and abdominal arterial aneurysms and/or dissections, as well as skeletal anomalies (chest abnormalities, scoliosis, joint laxity, arachnodactyly). LDS is divided into LDS type I and LDS type II based on the phenotype, then further categorized depending on the causative gene. Both LDS type I and II involve the cardiovascular and skeletal manifestations mentioned above. In addition, LDS type I involves craniofacial manifestations including hypertelorism, bifid uvula/cleft palate, and craniosynostosis. LDS type I caused by a TGFBR1 mutation is known as LDS1A, whereas LDS type I caused by a TGFBR2 mutation, is known as LDS1B. LDS type II has cutaneous manifestations including velvety and translucent skin, easy bruising, widened and atrophic scars, and uterine rupture. LDS type II caused by a TGFBR1 mutation is known as LDS2A, whereas LDS type II caused by a TGFBR2 mutation is known as LDS2B. Identical mutations can lead to LDS type I or type II, supporting the belief that both types are part of a clinical continuum. Mutations in the TGFBR2 gene have also been identified in conditions with phenotypic overlap with LDS. Marfan syndrome (MFS) is a systemic connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. MFS is most often associated with mutations in the FBN1 gene; however some individuals who meet, or nearly meet, the clinical diagnostic criteria for MFS have been shown to have mutations in TGFBR2. Familial thoracic aortic aneurysm and dissection (TAAD), which involves cardiovascular manifestations only, has also been associated with mutations in TGFBR2. Shprintzen-Goldberg syndrome, a rare disorder characterized by marfanoid habitus, cardiovascular anomalies, mental retardation, and craniosynostosis, has been associated with a TGFBR2 mutation. TGFBR2 mutations have also been identified in individuals who phenotypically presented with vascular type Ehlers-Danlos syndrome (EDS), but tested negative for COL3A1 mutations (the gene typically associated with vascular EDS). Transforming growth factor-beta receptor II (TGFBR-II) is a 70 to 80 kDa protein that belongs to the serine-threonine kinase family of cell surface receptors. This group of receptors regulates a variety of cellular processes including proliferation, differentiation, cell cycle arrest, apoptosis, and formation of the extracellular matrix. Receptor activation occurs upon binding of transforming growth factor-beta (TGF) to TGFBR-II, which then recruits and phosphorylates TGFBR-I, propagating the signal to downstream transcription factors. TGFBR-II is encoded by the TGFBR2 gene, which contains 7 exons plus 2 variant exons and is located on chromosome 3p22. Excluding TGFBR2 mutations reported in malignancies, more than 50 pathogenic TGFBR2 mutations have been associated with the syndromic features described above. The majority of these are missense mutations, although splice site and nonsense mutations have also been reported. The great majority of pathogenic mutations are located in the intracellular serine/threonine kinase domains. Few genotype-phenotype correlations exist for TGFBR2 mutations; indeed, identical mutations have been reported to cause MFS in some individuals and LDS in others. Approximately 25% of individuals with LDS have an affected parent,
while 75% have a de novo mutation. TGFBR2 mutations can manifest with a range of phenotypes and variable ages of onset both between families and among affected members of the same family. Thus, TGFBR2-related disorders can be diagnostically challenging. Genetic testing for TGFBR2 mutations allows for the confirmation of a suspected genetic disease. Confirmation of LDS or other TGFBR2-associated genetic diseases allows for proper treatment and management of the disease, and preconception/prenatal and family counseling. For example, in LDS, aortic dissection has been observed at aortic dimensions that do not confer risk in MFS caused by FBN1 mutations. Therefore, a more aggressive treatment strategy or earlier surgical intervention might be considered if an individual were found to have a TGFBR2 mutation rather than an FBN1 mutation.

**Useful For:** Aiding in the diagnosis of TGFBR2-associated Loeys-Dietz syndrome, Marfan or Marfan-like syndrome, familial thoracic aortic aneurysm and dissection syndrome, and Shprintzen-Goldberg syndrome

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Thalassemia and Hemoglobinopathy Evaluation**

**Clinical Information:** The thalassemias are a group of autosomal recessive disorders of hemoglobin (Hb) synthesis. Normal adult Hb consists of 2 alpha globin chains (encoded by 2 pairs of alpha globin genes, each pair located on 1 of the chromosomes 16), and 2 beta globin chains (encoded by 2 beta globin genes, each located on 1 of the chromosomes 11). Thalassemia syndromes result from an underproduction of 1 or 2 types of globin chains and are characterized by the type (alpha, beta, delta) and magnitude of underproduction (number of defective genes) and the severity of clinical symptoms (minor, major). The severity of the clinical and hematologic effects is directly related to the number of genes deleted or affected. The most common form of thalassemia is heterozygous alpha thalassemia 2, with 1 affected alpha globin gene. In heterozygous alpha thalassemia 2, there is no clinical effect and the blood count, including the mean cell volume, is normal. Heterozygous alpha thalassemia 1 and homozygous alpha thalassemia 2 (both with 2 affected genes) have the typical thalassemic picture (eg, hypochromic microcytic anemia, pallor, fatigue, shortness of breath, jaundice, and splenomegaly). Hemoglobin H (Hb H) disease, having a deletion of 3 alpha chains, is a moderate-to-severe hemolytic disease. The severity of Hb H disease is related to the amount of Hb H in the red cells. The morphology of the red cells is often very bizarre due to denatured Hb found within the red cells. The deletion of all 4 alpha chains is incompatible with life. Affected fuses are hydropic and die in utero or shortly after premature birth. The blood smears show large hypochromic red cells, nucleated red cells, target cells, and red cell fragments. Hb Barts, Hb H, and Hb Portland are present in significant quantities. It is the most common cause of hydrops fetalis in Southeast Asia and southern China. This consultative study tests for the detection of alpha-thalassemias, beta-thalassemias, delta-beta-thalassemia, and for Hb variants that are commonly accompanied by thalassemias: Hb H, Hb Lepore, Hb Barts, unstable Hb, hemolytic anemias, Hb E, hereditary persistence of high fetal Hb (several varieties), and combinations of Hb S with alpha- or beta-thalassemia, Hb E/beta-O-thalassemia, and many other complex thalassemic disorders. Some of the alpha-thalassemias (eg, Hb H disease) can be reliably identified by Hb electrophoresis alone; some require DNA probe studies. Since iron deficiency can mimic thalassemias, ferritin levels are measured to evaluate

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this possibility.

**Useful For:** Diagnosis of thalassemia

**Interpretation:** A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

**Reference Values:**
Definitive results and an interpretive report will be provided.


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**TLU 8603**

**Thallium, 24 Hour, Urine**

**Clinical Information:** Thallium is found in some depilatories and rodenticides. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy and renal failure. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 g.

**Useful For:** Detecting toxic thallium exposure

**Interpretation:** Normal daily output is <1 mcg/day. Exposed patients can have urine output >10 mcg/day. The long-term consequences of such an exposure are poor.

**Reference Values:**
0-1 mcg/specimen
   Reference values apply to all ages.

**Clinical References:**

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**TLB 8149**

**Thallium, Blood**

**Clinical Information:** Thallium is a by-product of lead smelting. The clinical interest in thallium derives primarily from its use as a rodenticide since this is the most frequent route of human exposure. Thallium is rapidly absorbed via ingestion, inhalation, skin contact, and through the mucous membranes of the mouth, gastrointestinal tract, and lungs. It is considered to be as toxic as lead and mercury, with similar sites of action. The mechanism of action of thallium is: -Competition with potassium at cell receptors to affect ion pumps -Inhibition of DNA synthesis -Binds to sulfhydryl groups on proteins in neural axons -Concentrates in renal tubular cells and reacts with protein to cause necrosis Patients exposed to high doses of thallium (>1 g) present with alopecia (hair loss), peripheral neuropathy and seizures, and renal failure.

**Useful For:** Detecting toxic thallium exposure

**Interpretation:** Normal blood concentrations are <1 ng/mL. Significant exposure is associated with thallium in blood >10 ng/mL, and blood concentrations as high as 50 ng/mL. The long-term sequelae from such an exposure is poor.

**Reference Values:**
0-1 ng/mL
   Reference values apply to all ages.

**Clinical References:**
Thallium, Random, Urine

Clinical Information: Thallium is found in some depilatories and rodenticides. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy and renal failure. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 g.

Useful For: Detecting toxic thallium exposure

Interpretation: Normal daily output is <1 mcg/day. Exposed patients can have urine output >10 mcg/day. The long-term consequences of such an exposure are poor.

Reference Values:
0-1 mcg/L
Reference values apply to all ages.


Thallium/Creatinine Ratio, Random, Urine

Clinical Information: Thallium is found in some depilatories and rodenticides. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 gram.

Useful For: Detecting toxic thallium exposure

Interpretation: Patients exposed to high doses of thallium (>1 g) present with alopecia, peripheral neuropathy and seizures, and renal failure. Normal daily output is <1 mcg/day. Exposed patients can have urine output >10 mcg/day. The long-term consequences of such an exposure are poor.

Reference Values:
0-1 mcg/g Creatinine
Reference values apply to all ages.


THC Confirmation, MS, SP

Interpretation: Assay threshold: 1.0 ng/mL

Reference Values:
Negative

Units: ng/mL

Test Performed by: Medtox Laboratories, Inc.
402 W. County Road D
St. Paul, MN 55112
Theophylline, Serum

**Clinical Information:** Theophylline and its congener, aminophylline, are used to relax smooth muscles of the bronchial airways and pulmonary blood vessels to relieve and prevent symptoms of asthma and bronchospasm. Theophylline is administered orally at a dose of 400 mg/day or 6 mg/kg, whichever is lower, or intravenously as aminophylline at 0.6 mg/kg/hour. Oral dosage may be increased at 200-mg increments to a maximum of 900 mg/day, or 13 mg/kg if the steady-state blood concentration is within the therapeutic range of 8.0 to 20.0 mcg/mL. Theophylline has a half-life of 4 hours in children and adult smokers, and 7 hours in nonsmoking adults, thus steady-state is reached in approximately 1 day. The volume of distribution is 0.5 L/kg, and the drug is approximately 50% protein bound. Theophylline exhibits zero-order clearance kinetics like phenytoin, small increases in dose yield disproportionately large increases in blood concentration. Co-administration of cimetidine and erythromycin will significantly inhibit theophylline clearance, requiring dosage reduction. Other drugs such as allopurinol, ciprofloxacin, oral contraceptives, and propranolol inhibit theophylline clearance to a lesser degree. Smoking induces the synthesis of cytochrome P448, the antipyrine-dependent cytochrome, which significantly increases the rate of metabolism of theophylline. Drugs such as phenobarbital, phenytoin, carbamazepine, and rifampin slightly increase the rate at which the drug is cleared. Theophylline exhibits rather severe toxicity that is proportional to blood level.

**Useful For:** Assessing and adjusting dosage for optimal therapeutic level Assessing toxicity

**Interpretation:** Response to theophylline is directly proportional to serum level. Patients usually receive the best response when the level is >8.0 mcg/mL, with minimal toxicity experienced as long as the level is < or =20.0 mcg/mL.

**Reference Values:**
Therapeutic:
- Bronchodilation: 8.0-20.0 mcg/mL
- Neonatal apnea (< or =4 weeks old): 6.0-13.0 mcg/mL
- Critical value: >20.0 mcg/mL

**Clinical References:**

Therapeutic Antibody by Flow Cytometry

**Clinical Information:** Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical diagnostic information. Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example:
- Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders -Anti-CD49d: estimates prognosis for B-cell chronic lymphocytic leukemia patients This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels. For the most appropriate interpretation, the requesting physician must provide the laboratory with: -The therapeutic monoclonal antibody being used or considered -The pertinent hematologic diseases that have been diagnosed or considered -Any pertinent protocol requirements
Useful For: Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets. Determining the eligibility of patients for monoclonal antibody therapies. Monitoring response to the therapeutic antibody.

Interpretation: The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

Reference Values:
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.

Clinical References:

Thermoactinomyces vulgaris, IgG Antibodies, Serum

Clinical Information: Thermoactinomyces vulgaris is one of the causative agents of hypersensitivity pneumonitis (HP). Other causative microorganisms include Micropolyspora faeni and Aspergillus fumigatus. The development of HP caused by Thermoactinomyces vulgaris is accompanied by an immune response to Thermoactinomyces vulgaris antigens with production of IgG antibodies. While the immunopathogenesis of HP is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.

Useful For: Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Thermoactinomyces vulgaris.

Interpretation: Elevated concentrations of IgG antibodies to Thermoactinomyces vulgaris, Aspergillus fumigatus, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

Reference Values:
- 0-12 years: < or =6.6 mg/L
- 13-18 years: < or =11.0 mg/L
- >18 years: < or =23.9 mg/L

Clinical References:

Thiamin (Vitamin B1), Whole Blood

Clinical Information: Thiamin (vitamin B1) is an essential vitamin required for carbohydrate metabolism, brain function, and peripheral nerve myelination. Thiamin is obtained from the diet. Body stores are limited and deficiencies can develop quickly. The total thiamin pool in the average adult is about 30 mg. An intake of 0.5 mg per 1,000 kcal per day is needed to maintain this pool. Due to its relatively short storage time, marginal deficiency can occur within 10 days and more severe deficiency within 21 days if intake is restricted. Approximately 80% of all chronic alcoholics are thiamin deficient.
due to poor nutrition. However, deficiency also can occur in individuals who are elderly, have chronic gastrointestinal problems, have marked anorexia, are on cancer treatment, or are receiving diuretic therapy. The signs and symptoms of mild-to-moderate thiamin deficiency are nonspecific and may include poor sleep, malaise, weight loss, irritability, and confusion. Newborns breast fed from deficient mothers may develop dyspnea and cyanosis; diarrhea, vomiting, and aphonia may follow. Moderate deficiency can affect intellectual performance and well-being, despite a lack of apparent clinical symptoms. Severe deficiency causes congestive heart failure (wet beriberi), peripheral neuropathy (dry beriberi), Wernicke encephalopathy (a medical emergency that can progress to coma and death), and Korsakoff syndrome (an often irreversible memory loss and dementia that can follow). Rapid treatment of Wernicke encephalopathy with thiamin can prevent Korsakoff syndrome. Symptoms of dry beriberi include poor appetite, fatigue, and peripheral neuritis. Symptoms of wet beriberi include cardiac failure and edema. Patients with Wernicke encephalopathy present with behavior change (confusion, delirium, apathy), diplopia (often sixth nerve palsies), and ataxia. A late stage, in which the patients may develop an irreversible amnestic confabulatory state, is referred to as the Wernicke-Korsakoff syndrome. The response to thiamin therapy in deficient patients is usually rapid. Thiamin deficiency is a treatable, yet underdiagnosed, disorder in the United States. A heightened level of awareness of the possibility of thiamin deficiency is necessary to identify, intervene, and prevent thiamin deficiency's dire consequences. It appears that no conditions are directly attributable to thiamin excess and that thiamin administration is safe except in extremely rare cases of anaphylaxis from intravenous thiamin. Whole blood thiamin testing is superior to currently available alternative tests for assessing thiamin status. Serum or plasma thiamin testing suffers from poor sensitivity and specificity, and <10% of blood thiamin is contained in plasma. Transketolase determination, once considered the most reliable means of assessing thiamin status, is now considered an inadequate method. The transketolase method is an indirect assessment. Since transketolase activity requires thiamin, decreased transketolase activity is presumed to be due to the decrease of thiamin. However, the test is somewhat nonspecific, as other factors may decrease transketolase activity. Transketolase is less sensitive than HPLC, has poor precision, and specimen stability concerns. Thiamin diphosphate is the active form of thiamin and is most appropriately measured to assess thiamin status. Thiamin diphosphate in circulating blood is present in erythrocytes, but is undetectable (present in very low levels) in plasma or serum. HPLC analysis of thiamin diphosphate in whole blood or erythrocytes is the most sensitive, specific, and precise method for determining the nutritional status of thiamin and is a reliable indicator of total body stores. This assay specifically targets and quantitates the active form of vitamin B1 (thiamin diphosphate) as an indicator of vitamin B1 status.

Useful For: Assessment of thiamin deficiency Thiamin measurement in patients with behavioral changes, eye signs, gait disturbances, delirium, and encephalopathy; or in patients with questionable nutritional status, especially those who appear at risk and who also are being given insulin for hyperglycemia

Interpretation: Values for thiamin diphosphate <70 nmol/L are suggestive of thiamin deficiency.

Reference Values:
70-180 nmol/L

Clinical References:
58, 59, and 68) can result in both low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), as well as invasive carcinoma.(1,2) Patients with both negative cytology and negative HPV have been shown to be at extremely low risk for cervical neoplasia.(1,2) For women 30 years and older who have received a negative Pap test and concurrent negative HPV result, the American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) recommendations for cervical screening state that physicians may lengthen the screening interval to 3 years when using the combined tests. Patients deemed to be at high risk by the clinician should still be screened more frequently. The presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a high-grade squamous intraepithelial lesion. Current guidelines for follow-up of a cytology-negative/HPV-positive patient recommend repeat HPV testing in 12 months.(2) Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). (1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV genotypes (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

**Useful For:** Detection of cervical carcinoma or intraepithelial lesions and the presence or absence of high-risk human papillomavirus (HR-HPV) in women over age 30 at risk for cervical neoplasia HPV testing detection of high risk genotypes associated with the development of cervical cancer Results can be used as an aid in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive HR-HPV but negative Pap smear results

**Interpretation:** Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized.
Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:
ThinPrep PAP Test:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

HPV Test:
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References:

83343
ThinPrep Diagnostic with Human Papillomavirus (HPV) Reflex
Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASC-US) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions and HSIL, as well as invasive carcinomas. Patients with HSIL have a greater risk for progression to carcinoma. In the setting of an abnormal Pap result, the presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, considering ordering this test, which is diagnostic, rather than the screen (83342 / ThinPrep Screen with Human Papillomavirus [HPV] Reflex). Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). (1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types
HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.

Useful For: Management and triage of patient’s, age 21 or greater, with abnormal Pap results Human papillomavirus (HPV) testing detection of high-risk genotypes associated with the development of cervical cancer Results can be used as an aid in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive high risk HPV (HR-HPV) but negative Pap smear results.

Interpretation: Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:
ThinPrep Pap Test:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

HPV Test:
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68


**82039 ThinPrep Diagnostic Without Physician Interpretation**

**Clinical Information:** The ThinPrep Pap test is an alternative preparation method for the cervical Pap screening test. The method utilizes a liquid-based technique that replaces the direct smear method of the conventional Pap screen. This method is 1 of several technologies developed to improve visualization of cellular material by reducing smearing trauma, air drying artifact, and obscuring blood and inflammation. In addition, variability in smearing technique is eliminated as the majority of processing and preparation is performed in the laboratory under controlled conditions. Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, this test should be ordered rather than 82037 / ThinPrep Screen, Without Physician Interpretation.

**Useful For:** Detection of cervical carcinoma or intraepithelial lesions when screening women for possible cervical neoplasia

**Interpretation:** Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Reference Values:**
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

**Note:** Abnormal results will be reviewed by a pathologist at an additional charge.

Clinical Information: The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), as well as invasive carcinomas. Patients with both a negative cytology and negative HPV have been shown to be at extremely low risk for cervical neoplasia. For women 30 years old and older who have received a negative Pap test and concurrent negative HPV result, the American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) recommendations for cervical screening state that physicians may lengthen the screening interval to 3 years when using the combined test. Patients deemed to be high risk by the clinician should still be screened more frequently. The presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a high-grade squamous intraepithelial lesion. Current guidelines for follow-up of a cytology-negative/HPV-positive patient recommend repeat HPV testing in 12 months. Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV's that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.
cervical neoplasia HPV testing detection of high-risk genotypes associated with the development of cervical cancer. Results can be used as an aid in triaging women with abnormal Pap smear results. Individual genotyping of HPV-16 or HPV-18, if present. Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive HR-HPV but negative Pap smear results.

**Interpretation:** Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

**Reference Values:**

**ThinPrep PAP Test:**
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

**HPV Test:**
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

**Clinical References:**
1. Lorincz AT, Richart RM: Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med 2003 August;127(8):959-968

83342 ThinPrep Screen with Human Papillomavirus (HPV) Reflex

**Clinical Information:** Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions and HSIL, as well as invasive carcinomas. Patients with HSIL have a greater risk for progression to carcinoma. In the setting of an abnormal Pap result, the presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, considering ordering the diagnostic test (83343/...
ThickPrep Diagnostic with Human Papillomavirus (HPV) Reflex) rather than this screen. Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

**Useful For:** Management and triage of patients, age 21 or greater, with abnormal Pap results HPV testing detection of high-risk genotypes associated with the development of cervical cancer Results can be used as an aid in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 and HPV-18, if present Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive HR-HPV but negative Pap smear results.

**Interpretation:** Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

**Reference Values:**
ThinPrep Pap Test:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.
HPV Test:
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References:

82037 ThinPrep Screen, Without Physician Interpretation

Clinical Information: The ThinPrep Pap test is an alternative preparation method for the cervical Pap screening test. The method utilizes a liquid-based technique that replaces the direct smear method of the conventional Pap screen. This method is 1 of several technologies developed to improve visualization of cellular material by reducing smearing trauma, air drying artifact, and obscuring blood and inflammation. In addition, variability in smearing technique is eliminated as the majority of processing and preparation is performed in the laboratory under controlled conditions. Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, considering ordering the diagnostic test 82039 / ThinPrep Diagnostic Without Physician Interpretation rather than this test.

Useful For: Detection of cervical carcinoma or intraepithelial lesions when screening women for possible cervical neoplasia

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

Clinical References:
4. Gay JD, Donaldson LD, Goellner JR: False-negative results in

**THCY**

**8619**

**Thiocyanate, Serum**  
**Clinical Information:** Nitroprusside (Nipride) is a rapid-acting hypotensive agent used to treat hypertensive crisis and to produce controlled hypotension during surgery. Nitroprusside reacts nonenzymatically with hemoglobin to produce 1 molecule of cyanometemoglobin and 4 molecules of free cyanide, which are converted by hepatic rhodanese to thiocyanate. Toxicity can result from excessive cyanide production resulting in hypoxia and metabolic acidosis. Accumulation of thiocyanate indicates that body stores of the reducing agent utilized by rhodanese to convert cyanide to thiocyanate may become depleted. In this situation, another antihypertensive drug should be considered.

**Useful For:** Monitoring toxicity in patients treated with nitroprusside

**Interpretation:** Thiocyanate, the major detoxification product of cyanide, can also be present in smokers. Nonsmokers may have concentrations between 1 and 4 mcg/mL compared with smokers who may have concentrations between 3 and 12 mcg/mL.

**Reference Values:**
- For nitroprusside therapy: < or =29 mcg/mL
- Toxicity: >50 mcg/mL


**FFTIO**

**57708**

**Thiocyanate, serum**  
**Reference Values:**
- Toxic thiocyanate concentrations: Greater than 10 mg/dL

**FFTHM**

**90354**

**Thiopental and Metabolite, Serum/Plasma**  
**Reference Values:**
- Reporting limit determined each analysis

  - Thiopental  
    - Synonym(s): Pentothal
    - Hypnotic range: 1 - 5 mcg/mL
    - Therapeutic coma: 30 - 100 mcg/mL
    - Anesthesia: 7 - 130 mcg/mL

  - Pentobarbital  
    - Synonym(s): Thiopental Metabolite

  - Peak serum concentrations of 1.2 - 3.1 mcg/mL were produced 0.5 - 2.0 hours after a 100 mg oral dose and peak serum concentrations of 3 mcg/mL were produced 6 min. following a 100 mg IV dose. Potentially toxic at blood concentrations greater than 10 mcg/mL.

**GTPMT**

**62753**

**Thiopurine Methyltransferase (TPMT) Genotyping, Blood**  
**Clinical Information:** The thiopurine drugs are purine antimetabolites that are useful in the treatment
of acute lymphoblastic leukemia, autoimmune disorders (eg, Crohn disease and rheumatoid arthritis), and organ transplant recipients. The thiopurine drugs, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), and azathioprine (AZA) are prodrugs that require intracellular activation to 6-thioguanine nucleotides (6-TGN). This activation is catalyzed by multiple enzymes. The cytotoxic effects of thiopurine drugs are achieved mainly through incorporation of 6-TGNs into DNA and RNA. The pathway that leads to synthesis of active cytotoxic 6-TGNs is in competition with inactivation pathways catalyzed by thiopurine methyltransferase (TPMT). Evaluation of this pathway is important because the levels of 6-TGNs measured in red blood cells have been correlated with both thiopurine therapeutic efficacy and toxicity such as myelosuppression. The distribution of TPMT activity in red blood cells is trimodal in Caucasian population, with approximately 0.3% of people having deficient (undetectable) TPMT activity, 11% low (intermediate) activity, and 89% normal TPMT activity. TPMT activity is inherited as a monogenic codominant trait and variable TPMT activity is associated with TPMT genetic variants. TPMT alleles,*3A (*3B and *3C), *3B, *3C, and *2, comprised of a combination of 3 different single nucleotide polymorphisms (c.460G>A, c.719A>G, and c.238G>C), account for the majority of inactivating alleles in some ethnicities, including Caucasians. Patients with genetically very low or absent TPMT activity who are treated with standard doses of these drugs are at risk for the development of life-threatening thiopurine toxicity. The US Food and Drug Administration, the Clinical Pharmacogenetics Implementation Consortium, and certain professional societies recommend consideration of TPMT genotype or TPMT erythrocyte testing prior to the initiation of therapy with thiopurine drugs. There is substantial evidence linking TPMT genotype to phenotypic variability. Dose adjustments based upon TPMT genotype have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings. Complementary clinical tests are available to measure TPMT enzymatic activity in erythrocytes. In general, genotyping will find 95% of the changes that impact TPMT activity and it is not impacted by other medications known to inhibit TPMT activity. This testing can be complimented by the TPMT erythrocyte phenotype testing if the clinician wants to check for lower TPMT enzyme activity, regardless of cause.

**Useful For:** Predicting potential for toxicity to thiopurine drugs (6-mercaptopurine, 6-thioguanine, and azathioprine)

**Interpretation:** Based on the genotype, an interpretative comment will be provided for the expected phenotype: Genotype: TPMT*1/*1: Genotype Comment: TPMT*2, *3A, *3B and *3C were not detected. This individual is most likely to have a TPMT*1/*1 genotype. Interpretation: This patient is most likely to have extensive (normal) TPMT activity. Genotype: TPMT*1/*2, TPMT*1/*3A, TPMT*1/*3B, TPMT*1/*3C: Genotype Comment: This individual is heterozygous for a deficient or inactive TPMT allele (*N). Interpretation: This patient is expected to have intermediate TPMT activity. Patients with intermediate TPMT activity can be treated with thiopurine drugs with fewer side effects by reducing the initial dose. Subsequent dose adjustments should be based on the degree of myelosuppression, according to disease-specific guidelines. Genotype: TPMT*2/*2, TPMT*3A/*3A, TPMT*3B/*3B, TPMT*3C/*3C: Genotype Comment: This individual is homozygous for a deficient or inactive TPMT allele (*N). Interpretation: This patient is expected to have poor (deficient) TPMT activity. In nonmalignant disease, treatment with thiopurine drugs is generally contraindicated for patients with poor (deficient) TPMT activity and alternative agents should be considered. For malignant diseases, drastically reduced doses may be used with subsequent dose adjustments based on degree of myelosuppression and according to disease-specific guidelines. Genotype: TPMT*2/*3A, TPMT*2/*3B, TPMT*2/*3C, TPMT*3A/*3B, TPMT*3A/*3C: Genotype Comment: This individual is compound heterozygous for deficient or inactive TPMT alleles (*N/*Z). Interpretation: This patient is expected to have poor (deficient) TPMT activity. In nonmalignant disease, treatment with thiopurine drugs is generally contraindicated for patients with poor (deficient) TPMT activity and alternative agents should be considered. For malignant diseases, drastically reduced doses may be used with subsequent dose adjustments based on degree of myelosuppression and according to disease-specific guidelines.

**Reference Values:**

An interpretive report is provided.

**Clinical References:**
Thiopurine Methyltransferase (TPMT) Genotyping, Saliva

Clinical Information: The thiopurine drugs are purine antimetabolites that are useful in the treatment of acute lymphoblastic leukemia, autoimmune disorders (eg, Crohn disease and rheumatoid arthritis), and organ transplant recipients. The thiopurine drugs, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), and azathioprine (AZA), are prodrugs that require intracellular activation to 6-thioguanine nucleotides (6-TGN). This activation is catalyzed by multiple enzymes. The cytotoxic effects of thiopurine drugs are achieved mainly through incorporation of 6-TGNs into DNA and RNA. The pathway that leads to synthesis of active cytotoxic 6-TGNs is in competition with inactivation pathways catalyzed by thiopurine methyltransferase (TPMT). Evaluation of this pathway is important because the levels of 6-TGNs measured in red blood cells have been correlated with both thiopurine therapeutic efficacy and toxicity such as myelosuppression. The distribution of TPMT activity in red blood cells is trimodal in Caucasian population, with approximately 0.3% of people having deficient (undetectable) TPMT activity, 11% low (intermediate) activity, and 89% normal TPMT activity. TPMT activity is inherited as a monogenic codominant trait and variable TPMT activity is associated with TPMT genetic variants. TPMT alleles, *3A (*3B and *3C), *3B, *3C, and *2, comprised of a combination of 3 different single nucleotide polymorphisms (c.460G>A, c.719A>G, and c.238G>C), account for the majority of inactivating alleles in some ethnicities, including Caucasians. Patients with genetically very low or absent TPMT activity who are treated with standard doses of these drugs are at risk for the development of life-threatening thiopurine toxicity. The US Food and Drug Administration, the Clinical Pharmacogenetics Implementation Consortium, and certain professional societies recommend consideration of TPMT genotype or TPMT erythrocyte testing prior to the initiation of therapy with thiopurine drugs. Dose adjustments based upon TPMT genotype have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings. Complementary clinical tests are available to measure TPMT enzymatic activity in erythrocytes. In general, genotyping will find 95% of the changes that impact TPMT activity and it is not impacted by other medications known to inhibit TPMT activity. This testing can be complimented by the TPMT erythrocyte phenotype testing if the clinician wants to check for lower TPMT enzyme activity regardless of cause.

Useful For: Predicting potential for toxicity to thiopurine drugs (6-mercaptopurine, 6-thioguanine, and azathioprine) Genotyping patients who prefer not to have their blood drawn

Interpretation: Based on the genotype, an interpretative comment will be provided for the expected phenotype. Genotype: TPMT*1/*1: Genotype Comment: TPMT*2, *3A, *3B, and *3C were not detected. This individual is most likely to have a TPMT*1/*1 genotype. Interpretation: This patient is most likely to have extensive (normal) TPMT activity. Genotype: TPMT*1/*2, TPMT*1/*3A, TPMT*1/*3B, TPMT*1/*3C: Genotype Comment: This individual is heterozygous for a deficient or inactive TPMT allele (*N). Interpretation: This patient is expected to have intermediate TPMT activity. Patients with intermediate TPMT activity can be treated with thiopurine drugs with fewer side effects by reducing the initial dose. Subsequent dose adjustments should be based on the degree of myelosuppression, according to disease-specific guidelines. Genotype: TPMT*2/*2, TPMT*3A/*3A, TPMT*3B/*3B, TPMT*3C/*3C: Genotype Comment: This individual is homozygous for a deficient or inactive TPMT allele (*N). Interpretation: This patient is expected to have poor (deficient) TPMT activity. In nonmalignant disease, treatment with thiopurine drugs is generally contraindicated for patients with poor (deficient) TPMT activity and alternative agents should be considered. For malignant diseases, drastically reduced doses may be used with subsequent dose adjustments based on degree of myelosuppression and according to disease-specific guidelines. Genotype: TPMT*2/*3A, TPMT*2/*3B, TPMT*2/*3C, TPMT*3A/*3B, TPMT*3A/*3C: Genotype Comment: This individual is compound heterozygous for deficient or inactive TPMT alleles (*N/*Z). Interpretation: This patient is expected to have poor (deficient) TPMT activity. In nonmalignant disease, treatment with thiopurine drugs is generally contraindicated for patients with poor (deficient) TPMT activity and alternative agents should
be considered. For malignant diseases, drastically reduced doses may be used with subsequent dose adjustments based on degree of myelosuppression and according to disease-specific guidelines.

**Reference Values:**
An interpretive report is provided.

**Clinical References:**

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**FATPM**

**Thiopurine Methyltransferase, RBC**

**Interpretation:** The TPMT, RBC assay is used as a screen to detect individuals with low and intermediate TPMT activity who may be at risk for myelosuppression when exposed to standard doses of thiopurines, including azathioprine (Imuran) and 6-mercaptopurine (Purinethol). TPMT is the primary metabolic route for inactivation of thiopurine drugs in the bone marrow. When TPMT activity is low, it is predicted that proportionately more 6-mercaptopurine can be converted into the cytotoxic 6-thioguanine nucleotides that accumulate in the bone marrow causing excessive toxicity. The activity of TPMT is measured by the nanomoles of 6-methylmercaptopurine (inactive metabolite) produced per 1 mL of packed red blood cells, (U/mL). TPMT phenotype testing does not replace the need for clinical monitoring of patients treated with thiopurine drugs. Genotype for TPMT cannot be inferred from TPMT activity (phenotype). Phenotype testing should not be requested for patients currently treated with thiopurine drugs. Current TPMT phenotype may not reflect future TPMT phenotype, particularly in patients who received blood transfusion within 30 - 60 days of testing. TPMT enzyme activity can be inhibited by several drugs such as: naproxen (Aleve), ibuprofen (Advil, Motrin), ketoprofen (Orudis), furosemide (Lasix), sulfasalazine (Azulfidine), mesalamine (Asacol), olsalazine (Dipentum), mfenamic acid (Ponstel), thiazide diuretics, and benzoic acid inhibitors. TPMT inhibitors may contribute to falsely low results: patients should abstain from these drugs for at least 48 hours prior to TPMT testing. Falsely low results may also occur as a result of inappropriate specimen handling and hemolysis.

**Reference Values:**
Normal TPMT activity:

24.0 – 44.0 U/mL: Individuals are predicted to be at low risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine therapy; no dose adjustment is recommended.

Intermediate TPMT activity:

17.0 – 23.9 U/mL: Individuals are predicted to be at intermediate risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine therapy; a dose reduction and therapeutic drug management is recommended.

Low TPMT activity:

Less than 17.0 U/mL: Individuals are predicted to be at high risk of bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine therapy; it is recommended to avoid the use of thiopurine drugs.

High TPMT activity:

Greater than 44.0 U/mL: Individuals are not predicted to be at risk for bone marrow toxicity (myelosuppression) as a consequence of standard thiopurine dosing, but may be at risk for therapeutic failure due to excessive inactivation of thiopurine drugs. Individuals may require higher than the normal standard dose. Therapeutic drug management is recommended.
### Thiosulfate, Urine

**Reference Values:**
Reporting limit determined each analysis

- **Creatinine (mg/L)**
  - U.S. Population (10th - 90th percentiles, median)
    - All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
    - Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
    - Females: 273 - 2170 mg/L, median 994 (n=11,635)

- **Thiosulfate (mcg/mL)**
  - Normal range: approximately 2.9 +/- 2.5 mcg/mL (based on an average creatinine concentration of 1 g/L)

- **Thiosulfate (Creatinine corrected) (mg/g Creat)**
  - Thiosulfate was detected in urine from 29 controls at 2.9 +/- 2.5 mg/g creatinine.
  - Exposure to 1240 nmol/L (30 ppm) for 45 minutes resulted in a urinary thiosulfate concentration of 60 mg/g creatinine.

### Specific Gravity Confirmation

**Physiologic range:** 1.010 - 1.030.

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### Thiothixene (Navane)

**Reference Values:**
Reference Range: 10.0 - 30.0 ng/mL

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### Thrombin Time (Bovine), Plasma

**Clinical Information:** Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: - Deficiency or functional abnormality (congenital or acquired) of many of the coagulation proteins - Deficiency or functional abnormality of platelets - Specific factor inhibitors - Acute disseminated intravascular coagulation - Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time and activated partial thromboplastin time are first-order tests for coagulation abnormalities and are prolonged in many disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. Thrombin catalyzes the transformation of fibrinogen to fibrin (by cleaving fibrinopeptides A and B), which is followed by polymerization of fibrin to form a clot. The thrombin time (TT) test measures the time of clot formation when thrombin is added to citrated plasma. The phospholipid-dependent procoagulant enzyme cascades (intrinsic, extrinsic, and "common" pathway) are bypassed by the addition of exogenous thrombin. Therefore, the TT mainly reflects functions and interactions of solution-phase exogenous thrombin and endogenous fibrinogen.

**Useful For:** The main utility of the thrombin time test is to detect or exclude the presence of heparin or heparin-like anticoagulants (which act by enhancing antithrombin's inhibition of thrombin and other procoagulant enzymes) when used in conjunction with the reptilase time (RT) in evaluating unexplained prolonged clotting times. Identifying the cause of a prolonged prothrombin time, activated partial thromboplastin time, or dilute Russell's viper venom time when used in conjunction with the RT and fibrinogen assay

**Interpretation:** Prolongation of the thrombin time (TT) is consistent with the presence of heparin-like
anticoagulants, hypofibrinogenemia, dysfibrinogenemia, fibrin degradation products, and antibody inhibitors of thrombin. An immeasurably prolonged TT is usually the result of heparin in the specimen or, rarely, the presence of thrombin antibodies or afibrinogenemia. When the TT test is performed with diluted bovine thrombin to achieve a normal plasma clotting time of about 20 seconds, the TT is capable of detecting unfractionated heparin at a concentration of 0.05 units/mL of heparin. Other tests useful in interpreting the significance of prolongation of the TT include: reptilase time (RT), human thrombin time, clottable fibrinogen assay, and the fibrin D-dimer assay. These tests are available as components of coagulation profile test panels. As seen in the following table, RT can help distinguish among the various causes of a prolonged TT. Thrombin Time Reptilase Time Causes Remarks Prolonged Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay

**Reference Values:**
15-23 seconds

**Clinical References:**

**FFTAT**
**Thrombin-Antithrombin Complex**
**Reference Values:**
<4.3 ng/mL

Pre-analytical conditions such as a difficult draw may spuriously increase test results.

**THRMP**
**Thrombophilia Profile**
**Clinical Information:** Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia may include venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis), recurrent miscarriage, and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, stillbirth). Other possible clinical presentation includes arterial thrombosis (especially among patients <50 years of age) with no other risk factors for atherosclerotic arterial occlusive disease (diabetes mellitus, hypercholesterolemia, hypertension, or tobacco smoking) and aseptic necrosis of bone (eg, femoral head mandible). Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (eg, prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity deep vein thrombosis; this risk is unrelated to thrombophilia. Inherited thrombophilias include: Deficiency due to reduced plasma protein level or dysfunctional protein of: - Antithrombin - Protein C - Protein S - Dysfibrinogenemias (rare) - Activated protein C resistance due to the factor V R506Q (Leiden) mutation - Prothrombin G20210A mutation Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis. Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF and are of uncertain significance with respect to thrombosis risk. Acquired deficiencies of protein C and protein S
are also found in liver patients treated with oral anticoagulants (eg, warfarin, Coumadin) since both of these proteins are dependent upon the action of vitamin K for normal function. Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the level of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma) and the portion of bound protein S also rises leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

**Useful For:** Evaluating patients with thrombosis or hypercoagulability states Detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis Detecting a deficiency of antithrombin, protein C, or protein S Detecting activated protein C resistance (and the factor V R506Q [Leiden] mutation if indicated) Detecting the prothrombin G20210A mutation

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** College of American Pathologists Consensus Conference XXXVI: diagnostic issues in thrombophilia. Arch Pathol Lab Med. 2002;126:1277-1433

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**FFTP0**

**57822**

**Thrombopoietin (TPO)**

**Reference Values:**
7–99 pg/mL

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**THYM**

**82606**

**Thyme, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>

**Thyroglobulin Antibody, Serum**

**Clinical Information:** Thyroglobulin autoantibodies bind thyroglobulin (Tg), a major thyroid-specific protein. Tg plays a crucial role in thyroid hormone synthesis, storage, and release. Tg is not secreted into the systemic circulation under normal circumstances. However, follicular destruction through inflammation (thyroiditis and autoimmune hypothyroidism), hemorrhage (nodular goiter), or rapid disordered growth of thyroid tissue, as may be observed in Graves disease or follicular cell-derived thyroid neoplasms, can result in leakage of Tg into the blood stream. This results in the formation of autoantibodies to Tg (anti-Tg) in some individuals. The same processes also may result in exposure of other "hidden" thyroid antigens to the immune system, resulting in the formation of autoantibodies to other thyroid antigens, in particular thyroid peroxidase (TPO) (anti-TPO). Since anti-Tg and anti-TPO autoantibodies are observed most frequently in autoimmune thyroiditis (Hashimoto disease), they were originally considered to be of possible pathogenic significance in this disorder. However, the consensus opinion today is that they are merely disease markers. It is felt that the presence of competent immune cells at the site of thyroid tissue destruction in autoimmune thyroiditis simply predisposes the patient to form autoantibodies to hidden thyroid antigens. In individuals with autoimmune hypothyroidism, 30% to 50% will have detectable anti-Tg autoantibodies, while 50% to 90% will have detectable anti-TPO autoantibodies. In Graves disease, both types of autoantibodies are observed at approximately half these rates. The presence of anti-Tg, which occurs in 15% to 30% of thyroid cancer patients, could result in misleading Tg results. In immunometric assays, the presence of thyroid antibody can lead to false-low measurement; whereas it might lead to false-high results in competitive assays.

**Useful For:** As an adjunct in the diagnosis of autoimmune thyroid diseases: Hashimoto disease, postpartum thyroiditis, neonatal hypothyroidism, and Graves disease Identification of potentially unreliable serum thyroglobulin measurements by immunoassay in the follow-up of patients with differentiated follicular-cell derived thyroid carcinomas (for this application order HTG2 / Thyroglobulin, Tumor Marker, Serum or HTGR / Thyroglobulin, Tumor Marker Reflex to LC-MS/MS or Immunoassay)

**Interpretation:** Diagnosis of Autoimmune Thyroid Disease: Measurements of antithyroid peroxidase (TPO) have higher sensitivity and equal specificity to antithyroglobulin (anti-Tg) measurements in the diagnosis of autoimmune thyroid disease. Anti-Tg levels should, therefore, only be measured if anti-TPO measurements are negative, but clinical suspicion of autoimmune thyroid disease is high. Detection of significant titers of anti-Tg or anti-TPO autoantibodies is supportive evidence for a diagnosis of Graves disease in patients with thyrotoxicosis. However, measurement of the pathogenic antithyroid-stimulating hormone (TSH) receptor antibodies by binding assay (THYRO / Thyrotropin Receptor Antibody, Serum) or bioassay (TSI / Thyroid-Stimulating Immunoglobulin [TSI], Serum) is the preferred method of confirming Graves disease in atypical cases and under special clinical circumstances. Positive thyroid autoantibody levels in patients with high-normal or slightly elevated serum thyrotropin levels predict the future development of more profound hypothyroidism. Patients with postpartum thyroiditis with persistently elevated thyroid autoantibody levels have an increased likelihood of permanent hypothyroidism. In cases of neonatal hypothyroidism, the detection of anti-TPO or anti-Tg in the infant suggests transplacental antibody transfer, particularly if the mother has a history of autoimmune thyroiditis or detectable thyroid autoantibodies. The neonatal hypothyroidism is likely to be transient in
these cases. Thyroid Cancer Follow-up: Following therapy of differentiated follicular-cell derived thyroid cancer, patients with no residual thyroid tissue and no persistent or recurrent cancer will have undetectable or very low serum Tg levels. Persistently elevated or rising serum Tg levels, either on or off thyroxine replacement therapy, suggest possible tumor persistence or recurrence. However, if a patient also has measurable anti-Tg autoantibody levels, the results of serum Tg measurements may be unreliable. Anti-Tg may result in both falsely-low and, less commonly, falsely high serum Tg measurements. Therefore, in anti-Tg-positive patients, serum Tg measurements should not be used as the sole measurement for thyroid cancer follow-up and should be interpreted with caution. A thyroglobulin antibody result of <4.0 IU/mL is unlikely to cause clinically significant thyroglobulin assay interference. It is recommended that the thyroglobulin result be reviewed for concordance with clinical presentation.

**Reference Values:**

- <4.0 IU/mL

Reference values apply to all ages.

**Clinical References:**


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**Thyroglobulin Mass Spectrometry, Serum**

**Clinical Information:** Thyroglobulin (Tg) is a highly thyroid-specific large homodimeric glycoprotein (approximately 660 KDa). It contains 8% to 10% of carbohydrates and iodine. Thyroxine (T4) and triiodothyronine (T3) are synthesized on Tg within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 for secretion. Depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves' disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is highly organ-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during primary treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of >1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are <0.1 to 0.2 ng/mL, the risk of disease is <1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg >2 ng/mL is considered suspicious. There are 3 situations, when serum Tg measurement might be misleading: 1. Remnant thyroid tissue (see above, 0.5-1 ng/mL Tg per gram) 2. Antithyroglobulin autoantibodies (TgAB), which occur in 15% to 30% of thyroid cancer patients, can lead to false-low measurement in immunometric assays (most commonly used); in competitive assays they may cause false-high results. 3. Heterophile antibodies (HAB) are antibodies that are capable of interacting with the antibodies used in immunoassays, usually resulting in false-high measurements. Depending on the assay and the patient population, this can lead to erroneously high results in 0.1% to 3.0% of patients. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAB or HAB. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.
Useful For: Accurate measurement of serum thyroglobulin (Tg) in patients with known or suspected antithyroglobulin autoantibodies (TgAB) or heterophile antibodies (HAB). Reflex testing of samples with previously unknown TgAB status that prove TgAB positive during immunoassay testing. Rarely, in patients without thyroid cancer to assist in the differential diagnosis of early phase silent thyroiditis versus Graves’ disease (the mass spectrometry-based method would only be required if these patients have TgAB or HAB).

Interpretation: Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay limit of quantification <1 ng/mL; for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum antithyroglobulin autoantibodies (TgAB) should also be measured, preferably with a method that allows detection of low concentrations of TgAB (< or =20 kIU/L). If TgAB are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results. If the apparent Tg concentration is <1 ng/mL, the sample should be remeasured by mass spectrometry. This will allow confident detection of Tg in the presence of TgAB down to 0.5 ng/mL (risk of residual/recurrent disease <1-3%). Samples from patients with Tg concentrations >1 ng/mL (or 2 ng/mL; there is some discussion in the literature) might not require Tg measurement by mass spectrometry, because current guidelines suggest further work-up might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest at best when Tg is just above this threshold (3%-25%, rising in parallel with Tg concentrations up to 10 ng/mL) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, it might therefore also be useful to test TgAB positive samples by mass spectrometry, even if the Tg concentration is >1.0 ng/mL, but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. There are no routine tests that can detect heterophile antibodies in patient samples. An unexpected high result is usually the tip-off in this case, and should prompt remeasurement by mass spectrometry, which will provide a reliable result. It has been determined that the presence of Tg autoantibodies in serum can lead to underestimation of Tg concentration by immunoassay methods. When antibodies are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, 20% of specimens containing antibodies that are negative for Tg by immunoassay tested positive by liquid chromatography-tandem mass spectrometry (LC-MS/MS); no results over 3 ng/mL by LC-MS/MS were observed. In rare cases, when Tg is measured in patients with an intact thyroid gland who do not have thyroid cancer, substantial elevations will primarily be observed in very large goiters, highly active Graves disease, and, most pronounced, in the early phase of acute thyroiditis, when follicular destruction releases massive amounts of stored Tg into the circulation. Levels are often well above 100 ng/mL.

Reference Values:
Healthy individuals with intact, functioning thyroid: < or =33 ng/mL

The reference ranges listed below, however, are for thyroid cancer follow up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Ranges are based on best practice guidelines and the literature, which includes Mayo Clinic studies, and represent clinical decision levels.

Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.5-1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level.

Tg <0.5 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Undetectable Tg levels in athyrotic individuals on suppression therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer.

Tg > or =0.5 ng/mL to 2.0 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Tg levels of 0.5-2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer.
Tg 2.1 ng/mL to 9.9 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of 2.1-9.9 ng/mL in athyrotic individuals on suppression therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer.

Tg > or =10 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant (>25%) risk of clinically detectable recurrent papillary/follicular thyroid cancer.

**Clinical References:**

**Thyroglobulin, Tumor Marker Reflex to LC-MS/MS or Immunoassay**

**Clinical Information:** Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 KDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves' disease), or glandular destruction (eg, thyroiditis) larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of >1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after thyroid stimulating hormone (TSH) stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are <0.1 to 0.2 ng/mL, the risk of disease is <1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg >2 ng/mL is considered suspicious. The presence of anti-thyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to false low measurements; whereas it might lead to false high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

**Useful For:** Reporting of accurate thyroglobulin results, depending on the anti-thyroglobulin antibodies status of the patient Accurate measurement of serum thyroglobulin in patients with known or suspected anti-thyroglobulin autoantibodies or possible heterophile antibodies

**Interpretation:** Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive
immunoassay - limit of quantification <1 ng/mL; for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum anti-thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results. If the apparent Tg concentration is <1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow confident detection of Tg in the presence of TgAb down to 0.5 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations >1.0 ng/mL might not require Tg measurement by mass spectrometry, because current guidelines suggest further work-up might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, it might therefore also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is >1.0 ng/mL, but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of anti-thyroglobulin autoantibodies (TgAb), in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, some specimens containing TgAb which are negative for Tg by immunoassay tested positive by LC-MS/MS. Therefore, measuring of Tg by mass spectrometry is the preferred method in TgAb positive patients. The listed decision levels, are for thyroid cancer follow-up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Decision levels are based on best practice guidelines and the literature, which includes Mayo Clinic studies. Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.5 to 1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level. Thyroglobulin by Mass Spectrometry Tg <0.5 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of thyroid-stimulating hormone (TSH) levels, serial Tg measurements, and radioiodine ablation status. Undetectable Tg levels in athyrotic individuals on suppression therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.5 ng/mL to 2.0 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Tg levels of 0.5-2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =2.0 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels >10 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status.

**Reference Values:**
Thyroglobulin Antibody: <4.0 IU/mL

**Clinical References:** 1. Grebe SKG: Diagnosis and Management of Thyroid Carcinoma: A Focus on
Clinical Information: Thyroglobulin (Tg) is a 660,000 molecular weight glycoprotein produced exclusively by the follicular cells of the thyroid. It is secreted into the follicular lumen, where it serves as the precursor of, and storage reservoir for, thyroxine (T4) and triiodothyronine (T3). T4 and T3 are released after Tg is endocytosed and proteolytically degraded in the thyrocyte. Since Tg is produced only by follicular thyrocyte-derived cells, measurement of serum Tg levels in athyrotic patients enables detection of persistence, recurrence, or metastasis of differentiated thyroid carcinoma. In addition, because of the thyroid specificity of Tg, its measurement in biopsy specimens of nonthyroidal tissues may assist in confirming and localizing metastatic disease. In the most common type of thyroid cancer, papillary thyroid carcinoma (PTC), >80% of all thyroid cancer cases, most metastatic disease occurs in loco-regional lymph nodes in the neck, which are easily examined by ultrasound. Most suspicious nodes undergo ultrasonography-guided fine-needle aspiration (FNA) cytology to determine a diagnosis. Unfortunately, in up to 20% of the specimens, inadequate cellularity or nonrepresentative sampling precludes the diagnosis. Several studies have reported that the detection of Tg in fine needle aspiration (FNA)-needle washes improves the evaluation of suspicious lymph nodes in patients with differentiated thyroid carcinoma.[1-3] A recent study reported that a Tg cutoff of 1 ng/mL for FNA-needle wash specimens provided 100% sensitivity and 96.2% specificity for the detection of metastatic thyroid carcinoma in lymph nodes.[3] The diagnostic performance of needle wash Tg at the 1-ng/mL cutoff compared favorably with cytology (95.1% overall agreement) and allowed accurate diagnosis in 18 of the 19 cases in which cytology was nondiagnostic or not performed.[3] Additionally, when measuring Tg in FNA-needle wash specimens, the clinical performance of FNA Tg is unaffected by the presence of Tg antibodies, a frequent problem when measuring Tg levels in serum. Cytologic examination and measurement of Tg can be performed on the same specimen. To measure Tg, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination has been expelled from the needle for a smear or CytoTrap preparation. Tg levels are measured in the needle wash.

Useful For: An adjunct to cytologic examination of fine-needle aspiration specimens in athyrotic individuals treated for differentiated thyroid cancer, to confirm or exclude metastases in enlarged or ultrasonographically suspicious lymph nodes

Interpretation: In athyrotic patients with a history of differentiated thyroid carcinoma, a fine-needle aspiration thyroglobulin (FNA-Tg) value >1.0 ng/mL suggests the presence of metastatic differentiated follicular cell-derived thyroid carcinoma in the biopsied area. FNA-Tg measurements yield reliable results in most cases with nondiagnostic cytology, and are approximately equal in diagnostic accuracy to cytological examinations that are deemed sufficient for diagnosis.

Reference Values:
< or =1.0 ng/mL
This cutoff has been validated for total needle wash volumes of < or =1.5 mL of normal saline. If wash volumes are substantially larger, a lower cutoff might apply.


HTG2 62800

**Thyroglobulin, Tumor Marker, Serum**

**Clinical Information:** Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 KDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone: TSH level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Grave disease), or glandular destruction (eg, thyroiditis) larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of >1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are <0.1 to 0.2 ng/mL, the risk of disease is <1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg >2 ng/mL is considered suspicious. The presence of antithyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to false-low results; whereas it might lead to false-high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg- by mass spectrometry. Refer to TGMS / Thyroglobulin Mass Spectrometry, Serum for accurate sample analysis of patients who are known to be TgAb positive. If TgAb status is unknown, refer to HTGR / Thyroglobulin, Tumor Marker Reflex to LC-MS/MS or Immunoassay. When HTGR is ordered, TgAb testing is performed first. If TgAb is negative (<4.0 IU/mL), Tg is assayed by immunoassay (sensitive down to 0.1 ng/mL). If TgAb is positive, Tg is assayed by mass spectrometry (sensitive down to 0.5 ng/mL).

**Useful For:** Follow-up of patients with differentiated thyroid cancers after thyroidectomy and radioactive iodine ablation

**Interpretation:** Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay (limit of quantification <1.0 ng/mL); for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results if using an immunometric assay. If the apparent Tg concentration is <1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow accurate detection of Tg, in the presence of TgAb, down to 0.5 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations >1.0 ng/mL might not require Tg measurement by mass spectrometry, because current guidelines suggest further workup might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, therefore, it might also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is >1.0 ng/mL, but not above the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg
secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that
the presence of antithyroglobulin autoantibodies (TgAb), in serum can lead to underestimation of Tg
concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg
values may be underestimated by up to 60% in immunoassays. In addition, approximately 20% of
specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by LC-MS/MS.
Therefore, measuring of Tg by mass spectrometry is the preferred method in TgAb positive patients. The
decision levels listed below, are for thyroid cancer follow up of athyrotic patients and apply to
unstimulated and stimulated thyroglobulin measurements. Decision levels are based on best practice
guidelines and the literature, which includes Mayo Clinic studies. Decision levels for thyroid cancer
patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not
been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to
serum Tg concentrations 0.5 to 1.0 ng/mL per gram of remnant tissue, depending on the
thyroid-stimulating hormone (TSH) level. Tg <0.1 ng/mL: Tg levels must be interpreted in the context of
TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels <0.1 ng/mL in athyrotic
individuals on suppressive therapy indicate a minimal risk (<1-2%) of clinically detectable recurrent
papillary/follicular thyroid cancer. Tg > or =0.1 to 2.0 ng/mL: Tg levels must be interpreted in the context
of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 0.1 to 2.0 ng/mL in
athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent
papillary/follicular thyroid cancer. Tg 2.1 to 9.9 ng/mL: Tg levels must be interpreted in the context of
TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 2.1 to 9.9 ng/mL in
athyrotic individuals on suppressive therapy indicate an increased risk of clinically detectable recurrent
papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Tg levels must be interpreted in the context of
TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels > or =10 ng/mL in athyrotic
individuals on suppressive therapy indicate a significant risk (>25%) of clinically detectable recurrent
papillary/follicular thyroid cancer.

Reference Values:

THYROGLOBULIN, TUMOR MARKER
Athyrotic: <0.1 ng/mL
Intact thyroid < or =33 ng/mL

THYROGLOBULIN ANTIBODY
< 4.0 IU/mL
Reference values apply to all ages.

Clinical References: 1. Grebe SKG: Diagnosis and management of thyroid carcinoma: a focus on
serum thyroglobulin. Exp Rev Endocrinol Metab 2009;4:25-43 2. Cooper DS, Doherty GM, Haugen BR,
et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules
and differentiated thyroid cancer. Management guidelines for patients with thyroid nodules and
differentiated thyroid cancer: The American Thyroid Association Guidelines Taskforce. Thyroid
National Comprehensive Cancer Network (NCCN) guidelines for treatment of cancer by site: version
thyroglobulin in the management of differentiated thyroid cancer. Accessed June 2014 Available at
http://www.update.com

Thyroid Autoantibodies Profile, Serum
Clinical Information: See individual unit codes.

Useful For: See individual unit codes.

Interpretation: See individual unit codes.

Reference Values:

THYROGLOBULIN ANTIBODY
<4.0 IU/mL
Reference values apply to all ages.
THYROPEROXIDASE ANTIBODIES
<9.0 IU/mL
Reference values apply to all ages.

Clinical References: See individual unit codes.

THSCM
83633

Thyroid Function Cascade, Serum

Clinical Information: This test utilizes a cascaded testing procedure to efficiently evaluate and monitor functional thyroid status. The cascade begins with thyroid-stimulating hormone (TSH) as a screening assay. In patients with an intact pituitary-thyroid axis, TSH provides a physiologic indicator of the functional level of thyroid hormone activity. Increased TSH indicates inadequate thyroid hormone, and suppressed TSH indicates excess thyroid hormone. Transient TSH abnormalities may be found in seriously ill, hospitalized patients, so this is not the ideal setting to assess thyroid function. However, even in these patients, TSH works better than total thyroxine (an alternative screening test). When TSH is normal, no additional testing will be necessary. However, when the TSH result is abnormal, appropriate follow-up tests will automatically be performed. If TSH is <0.3 mIU/L or >4.2 mIU/L, free thyroxine (FT4) is performed. The supplemental measurement of FT4 in patients with abnormal TSH measurements allows one to better assess the severity of the changes. Serum triiodothyronine (T3) levels often are depressed in sick and hospitalized patients, caused in part by the biochemical shift to the production of reverse T3. Therefore, T3 generally is not a reliable predictor of hypothyroidism. However, in a small subset of hyperthyroid patients, hyperthyroidism may be caused by overproduction of T3 (T3 toxicosis). To help diagnose and monitor this subgroup, T3 is measured on all specimens with suppressed TSH and normal FT4 concentrations. Detectable concentrations of antithyroperoxidase (anti-TPO) antibodies are observed in patients with autoimmune thyroiditis and may cause the destruction of thyroid tissue, resulting in the eventual hypothyroidism. Anti-TPO antibodies are measured in all specimens with elevated TSH concentrations. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Screening for a diagnosis of thyroid disease

Interpretation: In primary hypothyroidism, thyroid-stimulating hormone (TSH) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation test with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

Reference Values:
0-5 days: 0.7-15.2 mIU/L
6 days-2 months: 0.7-11.0 mIU/L
3-11 months: 0.7-8.4 mIU/L
1-5 years: 0.7-6.0 mIU/L
6-10 years: 0.6-4.8 mIU/L
11-19 years: 0.5-4.3 mIU/L
>20 years: 0.3-4.2 mIU/L

Thyroid-Stimulating Hormone-Sensitive (s-TSH), Serum

Clinical Information: Thyroid-stimulating hormone (TSH, thyrotropin) is a glycoprotein hormone consisting of 2 subunits. The alpha subunit is similar to those of follicle-stimulating hormone, human chorionic gonadotropin, and luteinizing hormone. The beta subunit is different from those of the other glycoprotein hormones and confers its biochemical specificity. TSH is synthesized and secreted by the anterior pituitary in response to a negative feedback mechanism involving concentrations of free triiodothyronine and free thyroxine. Additionally, the hypothalamic tripeptide, thyrotropin-releasing hormone, directly stimulates TSH production. TSH interacts with specific cell receptors on the thyroid cell surface and gives rise to 2 main actions. First, it stimulates cell reproduction and hypertrophy. Second, it stimulates the thyroid gland to synthesize and secrete triiodothyronine and thyroxine. Serum TSH concentrations exhibit a diurnal variation with the peak occurring during the night and the nadir occurring between 10 a.m. and 4 p.m. This biological variation does not influence the interpretation of the test result since most clinical TSH measurements are performed on ambulatory patients between 8 a.m. and 6 p.m. When hypothalamic-pituitary function is normal, a log/linear inverse relationship between serum TSH and free thyroxine exists. To aid in ordering appropriate thyroid function testing, THSCM / Thyroid Function Cascade, Serum utilizes a cascaded testing procedure to efficiently evaluate and monitor functional thyroid status. Serum TSH is the first-line test and when the s-TSH result is abnormal, appropriate follow-up tests will automatically be performed. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Screening for thyroid dysfunction and detecting mild (subclinical), as well as overt, primary hypo- or hyperthyroidism in ambulatory patients Monitoring patients on thyroid replacement therapy Confirmation of thyroid-stimulating hormone (TSH) suppression in thyroid cancer patients on thyroid suppression therapy Prediction of thyrotropin-releasing hormone-stimulated TSH response

Interpretation: In primary hypothyroidism, thyroid-stimulating hormone (TSH) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamic) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

Reference Values:
0-5 days: 0.7-15.2 mIU/L
6 days-2 months: 0.7-11.0 mIU/L
3-11 months: 0.7-8.4 mIU/L
1-5 years: 0.7-6.0 mIU/L
6-10 years: 0.6-4.8 mIU/L
11-19 years: 0.5-4.3 mIU/L
>20 years: 0.3-4.2 mIU/L

Thyroid-Stimulating Immunoglobulin (TSI), Serum

**Clinical Information:** Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin receptor (thyroid-stimulating hormone receptor: TSHR), thyroid-peroxidase (TPO), and thyroglobulin (Tg), as well as an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. The role of the TPO and Tg autoantibodies in either autoimmune thyrotoxicosis or autoimmune hypothyroidism is less well established; they may merely represent epiphenomena. Detectable concentrations of anti-TPO antibodies are observed in most patients with autoimmune thyroid disease (eg, Hashimoto’s thyroiditis, idiopathic myxedema, and Graves disease). Autoantibodies that bind and transactivate the TSHR lead to stimulation of the thyroid gland independent of the normal feedback-regulated thyroid-stimulating hormone (TSH) stimulation. These TSHR autoantibodies also are known as long-acting-thyroid-stimulator or thyroid-stimulating immunoglobulins (TSI). Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. At least 20% of patients with autoimmune hypothyroidism also have evidence either of TSHR-blocking antibodies or, less commonly, TSI. TSHR autoantibodies may be found before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease are aimed at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent cure. TSI are IgG antibodies and can therefore cross the placental barrier, causing neonatal thyrotoxicosis.

First-order tests for autoimmune thyroid disease include TPO / Thyroperoxidase (TPO) Antibodies, Serum (most suited for suspected cases of autoimmune hypothyroidism) and THYRO / Thyrotropin Receptor Antibody, Serum. Thyrotropin receptor antibody (TSHR-antibody) is a binding assay that detects both TSI and TSHR-blocking autoantibodies; it can be used instead of this TSI assay for most applications, as long as the results are interpreted in the clinical context. The TSHR-antibody test has a shorter turnaround time than the TSI assay, is less expensive, and if interpreted within the clinical context, has excellent correlation with the TSI assay. Specific detection of TSI is accomplished by this second-order bioassay.

**Useful For:** Second-order testing for autoimmune thyroid disease, including: -Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical signs and/or contraindicated (eg, pregnant or breast-feeding) or indeterminate thyroid radioisotope scans -Diagnosis of clinically suspected Graves disease (eg, extrathyroidal manifestations of Graves disease: endocrine exophthalmos, pretibial myxedema, thyroid acropachy) but normal thyroid function tests -Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past Graves disease -Differential diagnosis of gestational thyrotoxicosis versus first trimester manifestation or recurrence of Graves disease -Assessing the risk of Graves disease relapse after anti-thyroid drug treatment A combination of TSI / Thyroid-Stimulating Immunoglobulin (TSI), Serum and THYRO / Thyrotropin Receptor Antibody, Serum is useful as an adjunct in the diagnosis of unusual cases of hypothyroidism (eg, Hashitoxicosis).

**Interpretation:** The sensitivity and specificity of an elevated thyroid-stimulating immunoglobulins (TSI) index for Graves disease diagnosis depends on whether patients have clinically active, untreated disease or disease treated with antithyroid drugs. Using a TSI index of 1.3 as the cutoff level in newly diagnosed, untreated patients, the sensitivity and specificity are >90%. For a higher cutoff of 1.8, specificity approaches 100%, but sensitivity decreases somewhat. In patients with inactive or treated Graves disease the specificity is similar, while sensitivity is lower, ranging from 50% to 80%. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has a TSI index of >3.9 during the last trimester, regardless of her remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. This is particularly relevant for women who have previously
undergone thyroid-ablative therapy or are on active antithyroid drug treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyroid-stimulating hormone receptor (TSHR) and transient changes in thyroid hormone protein binding, is not associated with an elevated TSI index. Finding an elevated TSI index in this setting suggests underlying Graves disease. An elevated TSI index at the conclusion of a course of anti-thyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TSI index, is not predictive of prolonged remission. In patients with thyroid function tests that fluctuate between hypo- and hyperthyroidism or vice versa, a clearly elevated TSHR-antibody level (>25%) and a simultaneous TSI index that is normal or only minimally elevated (1.3-1.8) suggest a diagnosis of possible Hashitoxicosis.

Reference Values:
< or =1.3 TSI index
Reference values apply to all ages.


Thyroid Peroxidase (TPO) Antibodies, Serum

Clinical Information: Thyroperoxidase (TPO) is an enzyme involved in thyroid hormone synthesis, catalyzing the oxidation of iodide on tyrosine residues in thyroglobulin for the synthesis of triiodothyronine and thyroxine (tetraiodothyronine). TPO is a membrane-associated hemoglycoprotein expressed only in thyrocytes and is one of the most important thyroid gland antigens. Disorders of the thyroid gland are frequently caused by autoimmune mechanisms with the production of autoantibodies. Anti-TPO antibodies activate complement and are thought to be significantly involved in thyroid dysfunction and the pathogenesis of hypothyroidism. The determination of TPO antibody levels is the most sensitive test for detecting autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease) and detectable concentrations of anti-TPO antibodies are observed in most patients with these disorders. The highest TPO antibody levels are observed in patients suffering from Hashimoto thyroiditis. In this disease, the prevalence of TPO antibodies is about 90% of cases, confirming the autoimmune origin of the disease. These autoantibodies also frequently occur (60%-80%) in the course of Graves disease. In patients with subclinical hypothyroidism, the presence of TPO antibodies is associated with an increased risk of developing overt hypothyroidism. Many clinical endocrinologists use the TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism, and Mayo Medical Laboratories endorses this practice. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Aiding in the diagnosis of thyroid autoimmune disorders Differentiating thyroid autoimmune disorders from nonautoimmune goiter or hypothyroidism As a diagnostic tool in deciding whether to treat a patient who has subclinical hypothyroidism

Interpretation: Values >9.0 IU/mL generally are associated with autoimmune thyroiditis, but elevations are also seen in other autoimmune diseases. In patients with subclinical hypothyroidism, the presence of thyroperoxidase (TPO) antibodies predicts a higher risk of developing overt hypothyroidism, 4.3% per year versus 2.1% per year in antibody-negative individuals. Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases, such as adrenal insufficiency and type 1 diabetes. The frequency of detectable anti-TPO observed in nonimmune thyroid disease is similar to the 10% to 12% observed in a healthy population with normal thyroid function. There is a good association between the presence of autoantibodies against TPO and histological thyroiditis. However, in view of the extensive regenerative capacity of the thyroid under the influence of thyroid-stimulating hormone, chronic thyroid disease may be present for years before the clinical manifestation of hypothyroidism becomes evident, if ever.
Reference Values:
<9.0 IU/mL
Reference values apply to all ages.


Thyrotropin Receptor Antibody, Serum

Clinical Information: Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin receptor (TSHR), thyroid peroxidase (TPO), and thyroglobulin (Tg), as well as by an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. These autoantibodies, also known as long-acting-thyroid-stimulator (LATS) or thyroid-stimulating immunoglobulins (TSI), bind to the receptor and transactivate it, leading to stimulation of the thyroid gland independent of the normal feedback-regulated thyrotropin (TSH) stimulation. Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. Some patients with autoimmune hypothyroidism also have evidence of either TSHR-blocking antibodies or, rarely, TSI. TSHR autoantibodies may be detected before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease are aimed at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent clinical cure. This is of particular relevance for pregnant women with a history of Graves disease that was treated with thyroid ablative therapy. Some of these women may continue to produce TSI. Since TSI are IgG antibodies, they can cross the placental barrier causing neonatal thyrotoxicosis. While the gold standard for thyroid-stimulating immunoglobulins is the bioassay (see TSI / Thyroid-Stimulating Immunoglobulin [TSI], Serum), the thyrotropin receptor antibody test has a shorter turnaround time, less analytical variability, and is less expensive.

Useful For: Recommended first-line test for detection of thyrotropin receptor (TSHR) antibodies, and used in the following situations: - Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical findings and/or contraindicated (eg, pregnant or breast-feeding) or nondiagnostic thyroid radioisotope scans - Diagnosis of clinically suspected Graves disease (eg, extrathyroidal manifestation of Graves disease include endocrine exophthalmos, pretibial myxedema, thyroid acropathy) in patients with normal thyroid function tests - Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past active Graves disease - Differential diagnosis of gestational thyrotoxicosis versus first trimester manifestation or recurrence of Graves disease - Assessing the risk of Graves disease relapse after antithyroid drug treatment

Interpretation: The sensitivity and specificity of an elevated thyrotropin receptor antibody (TRAb) test for Graves disease diagnosis depends on whether patients have disease treated with antithyroid drugs or clinically active, untreated disease. Based on a study that included specimens from 436 apparently healthy individuals, 210 patients with thyroid diseases without diagnosis of Graves disease, and 102 patients with untreated Graves disease, a decision limit of 1.75 IU/L showed a sensitivity of 97% and a specificity of 99% for detection of Graves disease. In healthy individuals and in patients with thyroid disease without diagnosis of Graves disease, the upper limit of antithyrotropin receptor (anti-TSHR) values are 1.22 IU/L and 1.58 IU/L, respectively (97.5th percentiles). A Mayo study of 115 patients, including 42 patients with Graves disease, showed a sensitivity of 95% and a specificity of 97% for detection of Graves disease at a decision limit of 1.75 IU/L. Assessment of TRAb status is particularly relevant in women who have undergone thyroid ablative therapy or are on active antithyroid treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Significant neonatal
thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has TRAb concentrations of >3.25 IU/L during the last trimester, regardless of her clinical remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the TSHR and transient changes in thyroid hormone protein binding, is only very rarely associated with an elevated TRAb test. Finding an elevated TRAb test in this setting suggests usually underlying Graves disease. An elevated TRAb test at the conclusion of a course of antithyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TRAb test, is not predictive of prolonged remission.

**Reference Values:**
< or =1.75 IU/L

**Clinical References:**

**TBGI**

**Thyroxine-Binding Globulin (TBG), Serum**

**Clinical Information:** Thyroxine binding globulin (TBG) is the high-affinity serum binding protein for thyroxine and triiodothyronine. Normally, the thyroid adjusts to changing concentrations of TBG by producing more or less thyroid hormone to maintain a constant level of metabolically important free hormone. Elevated TBG levels are associated with influences such as pregnancy, genetic predisposition, oral contraceptives, and estrogen therapy. TBG levels can decrease with androgenic or anabolic steroids, large doses of glucocorticoids, hypoproteinemic states, liver disease, nephrotic syndrome, and congenital TBG variants.

**Useful For:** Determination of thyroxine-binding globulin levels is particularly useful for cases in which total thyroid hormone levels do not correlate with the thyrometabolic status, most commonly with pregnancy or the use of contraceptive steroids

**Interpretation:** A change in thyroxine-binding globulin (TBG) concentration may be of hereditary, pathophysiologic, or pharmacologic origin. The TBG concentration indicates whether an abnormally high or low total thyroid hormone concentration is offset by a parallel increase or decrease in TBG concentration. In TBG deficiency, one may find euthyroid patients with extremely low total thyroxine (T4) values. Conversely, patients with high TBG levels may be clinically euthyroid with high serum total T4 values. Twenty-four specimens obtained during various stages of pregnancy yielded results ranging from 27 to 66 mcg/mL with a median of 43 mcg/mL. The literature suggests 47 to 59 mcg/mL as the range of TBG values expected during the third trimester of pregnancy.

**Reference Values:**
Males: 12-26 mcg/mL
Females: 11-27 mcg/mL

**Clinical References:**

**T4BPE**

**Thyroxine-Binding Protein Electrophoresis, Serum**

**Clinical Information:** Normally, almost all thyroxine (99.5%) is bound to thyroxine-binding globulin, prealbumin, and albumin. Deficiencies and aberrant forms of these binding proteins can occur, causing difficulties interpreting thyroid function test results. Such abnormalities may be identified by thyroxine-binding protein electrophoresis.

Current as of July 8, 2016 11:28 am CDT
Useful For: Explaining unusual thyroxine (T4), free T4, and thyroxine-binding globulin (TBG) test results that do not correlate with the patient’s clinical presentation. Detecting the presence of aberrant thyroxine-binding proteins such as abnormal forms of albumin and prealbumin. Detecting selective deficiency of one of the thyroxine-binding proteins. Detecting antibodies to T4. An adjunct to the diagnosis of patients with high T4 concentration due to peripheral hormone resistance by ruling out thyroxine-binding abnormalities.

Interpretation: Rare protein-binding abnormalities may be suspected in euthyroid patients having an elevated total thyroxine (T4) but normal thyroxine-binding globulin (TBG). The following example is from a healthy 40-year-old male with familial dysalbuminemic hyperthyroxinemia, a benign familial condition that can be confused with hyperthyroidism: -Increased T4 of 14.4 mcg/dL (normal=5.0-12.5 mcg/dL). -Normal TBG of 20.1 mcg/dL (normal=12-26 mcg/mL). The thyroxine-binding protein electrophoresis (TBPE) assay identified that of the saturating dose of (125)I-T4: -52% was bound to albumin (normal 12%-34%) -36% was bound to thyroxine-binding prealbumin (normal 49%-70%) -13% was bound to TBG (normal 10%-25%). In this example, based on the TBPE findings, this patient’s increased serum T4 was due to increased binding to albumin. This was suggestive of familial dysalbuminemic hyperthyroxinemia (FDH), an inherited abnormality characterized by the presence of a variant serum albumin with preferential affinity for T4.

Reference Values:
THYROXINE-BINDING PROTEIN ELECTROPHORESIS
10.3-24.9 mcg T4/dL bound to TBG
11.5-34.1 mcg T4/dL bound to albumin
48.8-70.4 mcg T4/dL bound to prealbumin

T4 (THYROXINE), TOTAL ONLY
Adult (> or =20 years): 4.5-11.7 mcg/dL
Pediatric:
0-5 days: 5.0-18.5 mcg/dL
6 days-2 months: 5.4-17.0 mcg/dL
3-11 months: 5.7-16.0 mcg/dL
1-5 years: 6.0-14.7 mcg/dL
6-10 years: 6.0-13.8 mcg/dL
11-19 years: 5.9-13.2 mcg/dL


FGTIA
Tiagabine (Gabitril), Serum
Reference Values:
Report Limit: 5.0 ng/mL
Reference Range: <235.0 ng/mL

Therapeutic and toxic ranges have not been established.

Peak concentrations are expected at 45 minutes post dose; steady state is generally attained within 2 days.

Observed tiagabine concentrations in clinical trials (30 â€“ 56 mg/day): <1 â€“ 234 ng/mL.

Measured tiagabine concentrations, post marketing (95% confidence interval): 0 â€“ 440 ng/mL.

Note: The 95% confidence interval for tiagabine concentrations determined by MEDTOX Laboratories will be updated periodically as more information becomes available.
Tick Analysis and Identification by PCR B. burgdorferi

Reference Values:
Negative

Tick-Borne Disease Antibodies Panel, Serum

Clinical Information: In North America, ticks are the primary vectors of infectious diseases.(1) Worldwide, ticks rank second only to mosquitoes in disease transmission. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic and granulocytic ehrlichiosis, babesiosis, tularemia, relapsing fever, and Colorado tick fever. Symptoms of the various tick-vectored diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A tick-borne panel can assist in identifying the pathogen, allowing treatment to be initiated. For information on the specific diseases, please see the individual unit codes.

Useful For: Evaluation of the most common tick-borne diseases found in the United States, including Lyme disease, human monocytic and granulocytic ehrlichiosis, and babesiosis Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms

Interpretation: See Individual Unit Codes

Reference Values:
Ehrlichia chaffeensis (HME) ANTIBODY, IgG
<1:64

Anaplasma phagocytophilum ANTIBODY, IgG
<1:64

Babesia microti IgG ANTIBODIES
<1:64

LYME DISEASE SEROLOGY
Negative


Tick-Borne Panel, Molecular Detection, PCR, Blood

Clinical Information: In North America, ticks are the primary vectors of infectious diseases.(1) Worldwide, ticks rank second only to mosquitoes in disease transmission. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic and granulocytic ehrlichiosis, babesiosis, tularemia, relapsing fever, Borrelia miyamotoi infection, and Colorado tick fever. Several of these diseases are transmitted by the same tick, and coinfections are occasionally seen. Symptoms of the various tick-vectored diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A tick-borne panel can assist in identifying the pathogen, allowing treatment to be initiated. Lyme disease is best detected through 2-tiered serologic testing. Acute ehrlichiosis, anaplasmosis, and babesiosis infections are best
diagnosed using molecular amplification methods that offer sensitive, specific, and rapid detection of these agents. For information on the specific diseases, see the individual tests.

**Useful For:** Evaluation of patients with suspected human monocytic and granulocytic ehrlichiosis, and babesiosis Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other non-specific symptoms

**Interpretation:** A positive LBAB / Babesia species, Molecular Detection, PCR, Blood test result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results, and clinical findings. A negative LBAB test result indicates absence of detectable DNA from Babesia species in the specimen, but does not always rule-out ongoing babesiosis in a seropositive person, since the parasitemia may be present at a very low level or may be sporadic. A positive EHRL / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood test result indicates the presence of specific DNA from Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis organism, or Anaplasma phagocytophilum, and support the diagnosis of ehrlichiosis or anaplasmosis. A negative EHRL test result indicates the absence of detectable DNA from any of these 4 pathogens in specimens, but does not exclude the presence of these organisms or active or recent disease. Since DNA of Ehrlichia ewingii is indistinguishable from that of Ehrlichia canis by this rapid PCR assay, a positive result for Ehrlichia ewingii/canis indicates the presence of DNA from either of these 2 organisms.

**Reference Values:**
- Babesia species, MOLECULAR DETECTION, PCR
  - Negative
- Ehrlichia/Anaplasma, MOLECULAR DETECTION, PCR
  - Negative


**FFTIC**

**Ticlopidine, Serum/Plasma**

**Reference Values:**
- Reporting limit determined each analysis

*Ticlopidine*

*Synonym(s): Ticlid*

Steady state peak plasma levels from patients on a 250 mg twice daily regimen: 0.22 ± 2.1 mcg/mL (mean of 0.99) at 2 hours post dose.

**FFTIL**

**Tilapia IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**
- <0.35 kU/L

**TIMG**

**Timothy Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FFTIB 91137**

**Tin, Blood**

**Reference Values:**

Reference Range: <5.0 ng/mL

Toxic range not established.

**FFTIN 91101**

**Tin, Serum**

**Reference Values:**

Reference Range: <5.0 ng/mL

Toxic range has not been established.

Note: Whole blood is the preferred specimen for monitoring exposure to tin.
Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. - CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ - CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ - CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for HLA DQ2 and/or DQ8) Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: The finding of tissue transglutaminase (tTG) IgA antibodies is specific for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is likely and the patient should undergo biopsy to confirm the diagnosis. The finding of tTG IgG antibodies may indicate a diagnosis of celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and the patient should undergo a biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of anti-tTG antibodies should begin to decrease within 6 to 12 months of onset of dietary therapy.
Reference Values:
TTG ANTIBODY, IgA
<4.0 U/mL (negative)
4.0-10.0 U/mL (weak positive)
>10.0 U/mL (positive)
Reference values apply to all ages.

TTG ANTIBODY, IgG
<6.0 U/mL (negative)
6.0-9.0 U/mL (weak positive)
>9.0 U/mL (positive)
Reference values apply to all ages.


Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions.

-CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free
Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Screening test for dermatitis herpetiformis, in conjunction with endomysial antibody test Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

**Interpretation:** The finding of tissue transglutaminase (tTG)-IgA antibodies is specific for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is likely and the patient should undergo biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of IgA-anti-tTG should begin to decrease within 6 to 12 months of onset of dietary therapy.

**Reference Values:**
- <4.0 U/mL (negative)
- 4.0-10.0 U/mL (weak positive)
- >10.0 U/mL (positive)

Reference values apply to all ages.

**Clinical References:**

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**Tissue Transglutaminase (tTG) Antibody, IgG, Serum**

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach.
to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet

**Useful For:** For individuals with IgA deficiency: -Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8 -Screening test for dermatitis herpetiformis, in conjunction with endomysial antibody test -Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

**Interpretation:** The finding of tissue transglutaminase (tTG) IgG antibodies may indicate a diagnosis of celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and the patient should undergo a biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of tTG-IgG antibodies should begin to decrease within 6 to 12 months of onset of dietary therapy. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

**Reference Values:**
- ≤6.0 U/mL (negative)
- 6.0-9.0 U/mL (weak positive)
- >9.0 U/mL (positive)
Reference values apply to all ages.


**Titanium, Serum**

**Clinical Information:** Titanium is the ninth most abundant element in the earth’s crust. Multiple oxidation states between 2+ and 4+ allow formation of a variety of compounds. There is no evidence that titanium is an essential element. Due in part to titanium’s oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic food-stuffs. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%) and the majority of ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lung. Titanium dust entering the respiratory tract is nonirritating and is almost completely nonfibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable serum titanium within the study group. While titanium concentrations are not a measure of toxicity, they are useful in determining whether implant breakdown is occurring. Serum titanium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium.
This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details

**Useful For:** Monitoring metallic prosthetic implant wear

**Interpretation:** Prosthesis wear is known to result in increased circulating concentration of metal ions. In the absence of an implant, circulating titanium is <1 ng/mL. Modest increase (1.0-3.0 ng/mL) in serum titanium concentration is evident with a prosthetic device in good condition. Serum concentrations >10 ng/mL in a patient with titanium-based implant suggest prosthesis wear. Increased serum titanium concentration in the absence of corroborating clinical information does not independently predict prosthesis wear or failure.

**Reference Values:**

0-1 ng/mL

**Clinical References:**

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**TNF-alpha (TNF-a) Serum**

**Reference Values:**

<5.6 pg/mL

**Clinical References:**


**TNFRSF1A Gene, Full Gene Analysis**

**Clinical Information:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a hereditary autoinflammatory disease that occurs most commonly, but not exclusively, in Northern European populations. TRAPS is characterized by recurrent febrile attacks and inflammation typically lasting 1 to 3 weeks. Accompanying clinical manifestations include abdominal pain, pleuritis, arthralgia, ocular involvement (conjunctivitis, periorbital edema, uveitis), myalgia, and cutaneous manifestations, usually migratory erythematous rash overlying areas of myalgia. Initial presentation most often occurs in childhood but age of onset can be variable and adult-onset cases have been described. Amyloid A (AA)-type amyloidosis is a serious long-term complication in some patients with TRAPS. TRAPS is caused by mutations in the TNFRSF1A gene, a tumor necrosis factor receptor. TRAPS is inherited in an autosomal dominant fashion with reduced penetrance. Mutations in TNFRSF1A account for approximately 32% to 50% of familial cases of TRAPS, while only 2% to 10% of sporadic cases have an identifiable mutation in this gene. Limited genotype-phenotype correlations have been described, but mutations in cysteine residues are more likely to be associated with amyloidosis. Patients with TRAPS often respond to corticosteroid treatment or anti-TNF therapy (etanercept) but are typically unresponsive to colchicine therapy.

**Useful For:** Confirmation of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) for patients with clinical features

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

An interpretive report will be provided.
Tobacco, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceeds as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Tobramycin, Peak, Serum

Clinical Information: Tobramycin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum
inhibitory concentration (MIC) of <4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of >8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of serum concentration during tobramycin therapy

**Interpretation:** Target peak concentrations depend on the type of infection being treated. Peak levels for most infections using conventional dosing are 3.0 to 12.0 mcg/mL. Prolonged exposure to peak concentrations exceeding 12.0 mcg/mL may lead to toxicity.

**Reference Values:**

**TOBRAMYCIN, PEAK**

Therapeutic: 3.0-12.0 mcg/mL  
Toxic: >12.0 mcg/mL

**TOBRAMYCIN, TROUGH**

Therapeutic: <2.0 mcg/mL  
Toxic: >2.0 mcg/mL

**Clinical References:**

**Tobramycin, Trough, Serum**

**Clinical Information:** Tobramycin is an antibiotic used to treat life-threatening blood infections by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of <4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of >8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequate clearance of tobramycin near the end of a dosing cycle

**Interpretation:** Goal levels depend on the type of infection being treated. Goal trough levels should be <2.0 mcg/mL for conventional (nonpulse) dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
- Therapeutic: <2.0 mcg/mL
- Toxic: >2.0 mcg/mL

**Clinical References:**

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**Toluene as Hippuric Acid, Occupational Exposure, Urine**

**Reference Values:**
- Creatinine: >50 mg/cL

Hippuric Acid is a metabolite of toluene and benzyl alcohol.

- Normal (unexposed population):
  - Average 0.8 g/L

- Exposed:
  - Biological Exposure Index (BEI):
    - 1.6 g/g creatinine (toluene exposure: end of shift)
  - Toxic: Not established

---

**Toluene, Occupational Exposure, Blood**

**Reference Values:**
- Units: mg/L

- Normal (unexposed population): None detected

- Exposed:
  - Biological Exposure Index (BEI): 0.05 mg/L (prior to last shift of workweek)
  - Biological Tolerance Value (BAT): 1.0 mg/L (end of exposure or end of shift)
Toxic:
Blood levels between 50 and 79 mg/L were found in people who died of acute toluene inhalation.

**FFTOL**

**Toluene, Occupational Exposure, Serum**

**Reference Values:**
Report limit: 0.02 mg/L

- Normal (Unexposed Population):
  - None Detected
- Exposed:
  - Not Established
- Toxic:
  - Not Established

**FMATG**

**Tomato IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.

This test should only be ordered by physicians who recognize the limitations of the test.

**TOMA**

**Tomato, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0      Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


TOPI

Topiramate, Serum

Clinical Information: Topiramate is a broad spectrum, anti-epileptic drug used to for various types of seizures, Lennox-Gastaut syndrome (a type of childhood onset epilepsy), and migraine prophylaxis. Topiramate blocks voltage-dependent sodium channels, potentiates gamma-aminobutyric acid (GABA) activity at some of the GABA receptors, and inhibits potentiation of the glutamate receptor and carbonic anhydrase enzyme which all contribute to its antiepileptic and antimigraine efficacy. In general, topiramate shows favorable pharmacokinetics with good absorption (1-4 hours for the immediate-release formulation), low protein binding, and minimal hepatic metabolism. Elimination is predominantly renal and it is excreted unchanged in the urine with an elimination half-life of approximately 21 hours. As with other anticonvulsant drugs eliminated by the renal system, patients with impaired renal function exhibit decreased topiramate clearance and a prolonged elimination half-life. Serum concentrations of other anticonvulsant drugs are not significantly affected by the concurrent administration of topiramate, with the exception of patients on phenytoin whose serum concentrations can increase after the addition of topiramate. Other drug-drug interactions include the coadministration of phenobarbital, phenytoin, or carbamazepine which can result in decreased topiramate concentrations. In addition, concurrent use of posaconazole and topiramate may result in the elevation of topiramate serum concentrations. Therefore, changes in co-therapy with these medications (phenytoin, carbamazepine, posaconazole, or phenobarbital) may require dose adjustment of topiramate and therapeutic drug monitoring could assist with this. The most common adverse drug effects associated with topiramate include: weight loss, loss of appetite, somnolence, dizziness, coordination problems, memory impairment, and paresthesia.

Useful For: Monitoring serum concentrations of topiramate Assessing compliance Assessing potential toxicity

Interpretation: Most individuals display optimal response to topiramate with serum levels 5.0 to 20.0 mcg/mL when used to control seizures. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Toxic levels have not been well established.

Reference Values:
Depends on clinical use:

Anticonvulsant (seizures): 5.0-20.0 mcg/mL
Psychiatry: 2.0-8.0 mcg/mL

Clinical Information: Toxoplasma gondii: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. (1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital Toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii. (2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. (3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. (4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual and audiologic defects. Rubella: Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. (5) Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. (6) Primary, in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, cardiovascular and ocular defects. (7) The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. (5) A total of 4 cases of rubella were reported to the CDC in 2011 without any cases of congenital rubella syndrome. (8) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (cdc.gov/rubella). Immunity may however wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella. Cytomegalovirus (CMV): CMV is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. (9) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation, or from a newly acquired infection. (10,11) Infection in these patient populations can affect almost any organ and lead to multi-organ failure. CMV is also responsible for congenital disease among newborns and is 1 of the ToRCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus [HSV]). CMV seroprevalence increases with age. In the United States the prevalence of CMV-specific antibodies increases from...
approximately 36% to over 91% in adolescents between the ages of 6 and 11 and adults over 80 years old, respectively. (12) Herpes Simplex Virus (HSV) Types 1 and 2: HSV types 1 and 2 are members of the Herpesviridae, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. (13) For example, the risk for reactivation is highest for HSV type 2 and the method of antiviral therapy may be different depending on the specific type of HSV causing disease. In addition, the results of HSV type specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery. (14, 15)

Useful For:
- Determination of immune status of individuals to the rubella virus following vaccination or prior exposure
- As an indication of past or recent infection with Toxoplasma gondii, cytomegalovirus, or herpes simplex virus (HSV)
- Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

**Interpretation:**
- **Toxoplasma gondii:** A positive Toxoplasma IgG result is indicative of current or past infection with Toxoplasma gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to Toxoplasma gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of Toxoplasma gondii infection subsequent to the first negative specimen. Recent or acute infection with Toxoplasma gondii can be evaluated with TOXMP / Toxoplasma gondii Antibody, IgM, Serum assay.
- **Rubella:** Positive: The presence of detectable IgG-class antibodies to rubella indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to rubella are considered immune. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies to rubella suggests no prior exposure to this virus or the lack of a specific immune response to immunization. Cytomegalovirus (CMV): Positive CMV IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional specimen for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV, and are therefore considered susceptible to primary infection. Herpes Simplex Virus (HSV): The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

**Reference Values:**

**Toxoplasma ANTIBODY, IgG**
- **Negative**
  - Toxoplasma IgG
    - $< or =9$ IU/mL (Negative)
    - $10-11$ IU/mL (Equivocal)
    - $> or =12$ IU/mL (Positive)

**RUBELLA ANTIBODY, IgG**
- **Vaccinated:** Positive ($> or =1.0$ AI)
- **Unvaccinated:** Negative ($< or =0.7$ AI)
**CYTOMEGALOVIRUS**

Negative

**HERPES SIMPLEX VIRUS (HSV), TYPE 1 AND TYPE 2 ANTIBODIES, IgG**

Herpes Simplex Virus (HSV) Type 1, IgG

Negative

Herpes Simplex Virus (HSV) Type 2, IgG

Negative


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**ToRCH Profile IgM, Serum**

**Clinical Information:** Toxoplasma gondii: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. (1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii. (2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. (3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. (4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the
infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Cytomegalovirus (CMV): CMV is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multi-organ failure. CMV is also responsible for congenital disease among newborns and is 1 of the ToRCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus; HSV). CMV seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 through 11 and adults over 80 years old, respectively. Herpes Simplex Virus (HSV): HSV types 1 and 2 are members of the Herpesviridae family of viruses and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections are routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. For example, the risk for reactivation is highest for HSV type 2 and the method of antiviral therapy may differ depending on the specific type of HSV-causing disease. In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.

**Useful For:** Aids in the diagnosis of both congenital and acute acquired toxoplasmosis, cytomegalovirus, and herpes simplex virus

**Interpretation:** Toxoplasma: Diagnosis of acute central nervous system, intrauterine, or congenital toxoplasmosis is difficult by routine serological methods. Active toxoplasmosis is suggested by the presence of IgM antibodies, but elevated anti-IgM titers are often absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by further testing at a toxoplasmosis reference laboratory or by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For confirmation of a diagnosis, the FDA issued a Public Health Advisory (7/25/1997) suggesting that sera found to be positive/equivocal for Toxoplasma gondii IgM antibody be sent to a Toxoplasma reference laboratory. The CDC or Jack Remington MD, Palo Alto Medical Foundation, 860 Bryant Street, Palo Alto, CA 94301 were recommended. (Reviewed 12/2011) Specimens interpreted as equivocal may contain very low levels of IgM. A second specimen should be drawn and tested. Cytomegalovirus (CMV): A negative CMV IgM result suggests that the patient is not experiencing a recent infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection, where the time of seroconversion is not well defined, as high as 28% (10/36) of pregnant women did not demonstrate CMV IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary rather than primary infections. Equivocal CMV IgM or IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if...
clinically indicated. Herpes Simplex Virus (HSV): The presence of IgM-class antibodies indicates recent infection

**Reference Values:**

Toxoplasma Ab, IgM

- Negative

Toxoplasma IgM Value
- <0.55 (negative)
- 0.55-<0.65 (equivocal)
- > or =0.65 (positive)

**CYTOMEGALOVIRUS, IgM**

- Negative (reported as positive, negative, or equivocal)

**HERPES SIMPLEX VIRUS, IGM**

- Negative (reported as positive or negative)

**Clinical References:**

**FFTOX**

**Toxocara Antibody, ELISA (Serum)**

**Reference Values:**

**REFERENCE RANGE:** Negative

Results of this assay must be interpreted with caution, as broad variations in antibody response occur, and levels may remain elevated for years after infection. Further, as with many parasitic serology assays, antibodies induced by other parasitic infections may crossreact in this assay. Although a negative result usually rules out infection with Toxocara spp., parallel testing of serial samples may prove useful in following patients with suspected Toxocara infection.

**TOXGP**

**Toxoplasma gondii Antibody, IgG, Serum**

**Clinical Information:** Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur,
leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

**Useful For:** Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii

**Interpretation:** A positive Toxoplasma IgG result is indicative of current or past infection with Toxoplasma gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed not to have had previous exposure to Toxoplasma gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of Toxoplasma gondii infection subsequent to the first negative specimen. Recent or acute infection with Toxoplasma gondii can be evaluated with the TOXMP / Toxoplasma gondii Antibody, IgM, Serum assay. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For further confirmation of a diagnosis, the FDA issued a Public Health Advisory (7/25/1997) suggesting that sera found to be positive/equivocal for Toxoplasma gondii IgM antibody be sent to a Toxoplasma reference laboratory. Recommended laboratories included the CDC or Jack Remington MD, Palo Alto Medical Foundation, 860 Bryant St., Palo Alto, CA 94301.

**Reference Values:**

- **Toxoplasma ANTIBODY, IgG**
  - Negative
  - \(< 9 \text{ IU/mL} \) (Negative)
  - \(10-11 \text{ IU/mL} \) (Equivocal)
  - \(> 12 \text{ IU/mL} \) (Positive)


**TOXOP**
61857
**Toxoplasma gondii Antibody, IgM and IgG (Separate Determinations), Serum**
**Clinical Information:** Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii. Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

**Useful For:** Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii

**Interpretation:** Active toxoplasmosis is suggested by the presence of IgM antibodies, but elevated anti-IgM titers are often absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. IgG is only indicative of previous exposure to Toxoplasma (recent or past). A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Seroconversion from negative to positive IgG is indicative of recent Toxoplasma gondii infection. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For further confirmation of a diagnosis, the FDA issued a Public Health Advisory (7/25/1997) suggesting that sera found to be positive/equivocal for Toxoplasma gondii IgM antibody be sent to a Toxoplasma reference laboratory. Recommended laboratories included the CDC or Jack Remington MD, Palo Alto Medical Foundation, 860 Bryant St., Palo Alto, CA 94301.

**Reference Values:**
Toxoplasma ANTIBODY, IgM
Negative

Toxoplasma IgM VALUE
<0.55 (Negative)
0.55 to <0.65 (Equivocal)
> or =0.65 (Positive)

Toxoplasma ANTIBODY, IgG
Negative

Toxoplasma IgG Value
< or =9 IU/mL (Negative)
10-11 IU/mL (Equivocal)
> or =12 IU/mL (Positive)

Toxoplasma gondii Antibody, IgM, Serum

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. (1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii. (2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. (3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. (4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

Useful For: Aids in the diagnosis of both congenital and acute acquired toxoplasmosis

Interpretation: Active toxoplasmosis is suggested by the presence of IgM antibodies, but elevated anti-IgM titers are often absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by further testing at a toxoplasmosis reference laboratory or by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For confirmation of a diagnosis, the FDA issued a Public Health Advisory (7/25/1997) suggesting that sera found to be positive/equivocal for Toxoplasma gondii IgM antibody be sent to a Toxoplasma reference laboratory; CDC or Jack Remington, MD, Palo Alto Medical Foundation, 860 Bryant Street, Palo Alto, CA 94301, were recommended. (Reviewed 12/2011) Specimens interpreted as equivocal may contain very low levels of IgM. A second specimen should be drawn and tested.

Reference Values:
Toxoplasma ANTIBODY, IgM
Negative

Toxoplasma IgM VALUE
<0.55 (Negative)
0.55 to <0.65 (Equivocal)
> or =0.65 (Positive)

Toxoplasma Gondii IgG and IgM, CSF

Reference Values:

Reference Range:

IgG:      <0.90
IgM:      <0.80

INTERPRETIVE CRITERIA:

IgG:

<0.90                Antibody not detected
0.9 – 1.09          Equivocal
> or = 1.10        Antibody detected

IgM:

<0.80                Antibody not detected
0.80 – 0.99        Equivocal
> or = 1.00        Antibody detected

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody form blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

Toxoplasma gondii, Molecular Detection, PCR

Clinical Information: Toxoplasma gondii is an intracellular protozoan parasite that chronically infects 10% or more of the adult population in the United States. Transmission may occur by ingestion of undercooked meat containing cysts, by direct contact with the feces of an infected cat excreting infectious oocysts, and vertically through the placenta. Accurate diagnosis is crucial because of the different therapeutic options. Serology is the traditional method for diagnosing toxoplasmosis and ascertaining the previous exposure history of the host. However, serology may be unreliable or challenging to interpret in immunocompromised patients and in suspected intrauterine infection. Detection of Toxoplasma gondii DNA by PCR has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis.

Useful For: Supporting the diagnosis of acute cerebral, ocular, disseminated, or congenital toxoplasmosis

Interpretation: A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA but do not exclude the presence of organism or active or recent disease.

Reference Values:

Negative

infects 10% or more of the adult population in the United States. Transmission may occur by ingestion of undercooked meat containing cysts, by direct contact with the feces of an infected cat excreting infectious oocysts, and vertically through the placenta. Accurate diagnosis is crucial because of the different therapeutic options. Serology is the traditional method for diagnosing toxoplasmosis and ascertaining the previous exposure history of the host.(1) Active toxoplasmosis is suggested by the presence of IgM antibodies, but elevated anti-IgM titers are often absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. Serologic results may also be unreliable or challenging to interpret in immunocompromised patients and in suspected intrauterine infection. Detection of Toxoplasma gondii DNA by PCR has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis. When performed on blood, it may detect circulating parasite DNA and thus confirm or support the results of serologic testing. PCR testing on peripheral blood has been used successfully to detect cases of ocular toxoplasmosis(2) as well as invasive disease in allogeneic stem cell recipients.(3,4)

Useful For: Supporting the diagnosis of active toxoplasmosis, particularly in immunocompromised individuals

Interpretation: A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA, but do not exclude the presence of organism or active or recent disease.

Reference Values:
Negative


TP53 Gene, Full Gene Analysis

Clinical Information: Li-Fraumeni syndrome (LFS) is a rare autosomal dominant hereditary cancer syndrome associated with germline mutations in the TP53 (also p53) gene. LFS is predominantly characterized by sarcoma (osteogenic, chondrosarcoma, rhabdomyosarcoma), young-onset breast cancer, brain cancer (glioblastoma), hematopoietic malignancies, and adrenocortical carcinoma in affected individuals. LFS is highly penetrant; the risk for developing an invasive cancer is 50% by age 30 and 90% by age 70 with many individuals developing multiple primary cancers. Childhood cancers are also frequently observed and typically include soft-tissue sarcomas, adrenocortical tumors, and brain cancer. Other reported malignancies include melanoma, Wilms tumor, kidney tumors, gonadal germ cell tumor, pancreatic cancer, gastric cancer, choroid plexus cancer, colorectal cancer, prostate cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, and thyroid cancer. There are published criteria for the use in establishing a clinical diagnosis of classic Li-Fraumeni syndrome and Li-Fraumeni-like (LFL) syndrome that include the above features listed. A larger percentage of families that meet the classic LFS criteria, are predicted to have a detectable mutation within the TP53 gene than families that meet the less strict LFL criteria (Birch's and Eeles' definitions).

Useful For: Confirmation of suspected clinical diagnosis of Li-Fraumeni syndrome or Li-Fraumeni-like syndrome Identification of familial TP53 mutation to allow for predictive testing in family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


**Tragacanth, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust, mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Tramadol and Metabolite, Urine**

**Clinical Information:** Tramadol, a centrally-acting opioid analgesic, is utilized in the treatment of moderate to moderately severe pain. Tramadol acts as an opiate agonist through the binding of the parent drug and its O-desmethyl (M1) metabolite to mu-opioid receptors and through the weak inhibition of norepinephrine and serotonin reuptake. The active metabolite, O-desmethyltramadol, is a considerably more potent mu-opioid receptor agonist than its parent drug. In urine, approximately 30% of tramadol is excreted as unchanged drug while approximately 60% is excreted as metabolites (N- and O-desmethyltramadol). The half-life of tramadol and O-desmethyltramadol is approximately 7 hours.

**Useful For:** Monitoring of compliance utilizing tramadol Detection and confirmation of the illicit use of tramadol

**Interpretation:** The presence of tramadol or O-desmethyltramadol >50 ng/mL is a strong indicator that the patient has used tramadol.

**Reference Values:**
Cutoff: <50 ng/mL


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**Transferrin, Serum**

**Clinical Information:** Transferrin is a glycoprotein with a molecular weight of 79570 daltons. It consists of a polypeptide strand with 2 N-glycosidically linked oligosaccharide chains and exists in numerous isoforms. The rate of synthesis in the liver can be altered in accordance with the body's iron requirements and iron reserves. Transferrin is the iron transport protein in serum. In cases of iron deficiency, the degree of transferrin saturation appears to be an extremely sensitive indicator of functional iron depletion. The ferritin levels are depressed when there is a deficiency of storage iron. In sideropenia, an iron deficiency can be excluded if the serum transferrin concentration is low, as in inflammation or less commonly, in cases of ascorbic acid deficiency. In screening for hereditary hemochromatosis, transferrin saturation provides a better indication of the homozygous genotype than does ferritin. The treatment of anemia with erythropoietin in patients with renal failure is only effective when sufficient depot iron is present. The best monitoring procedure is to determine transferrin saturation during therapy. Transferrin saturation in conjunction with ferritin gives a conclusive prediction of the exclusion of iron overloading in patients with chronic liver disease.

**Useful For:** Screening for chronic iron overload diseases, particularly hereditary hemochromatosis

**Interpretation:** Serum iron, total iron binding capacity (TIBC), and percent saturation are useful only in screening for chronic iron overload diseases, particularly hereditary hemochromatosis. Although serum iron, TIBC, and percent saturation are widely used for the diagnosis of iron deficiency, serum ferritin is a much more sensitive and reliable means of demonstrating iron deficiency. In hereditary hemochromatosis, serum iron is usually >150 mcg/dL and percent saturation exceeds 60%. In advanced iron overload states, the percent saturation often exceeds 90%.

**Reference Values:**
200-360 mg/dL

**Transforming Growth Factor beta, Serum**

**Interpretation:** Results are intended for research purposes or in attempts to understand the pathophysiology of unusual immune or inflammatory disorders.

**Reference Values:**
Transforming Growth Factor beta, S: 3,465 – 13,889 pg/mL

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**Transmembrane Activator and CAML Interactor (TACI) Gene, Full Gene Analysis**

**Clinical Information:** Transmembrane activator and CAML interactor (TACI) is a member of the tumor-necrosis factor (TNF)-like receptor family, a group of receptors that regulate both survival and apoptosis of immune cells. (1) TACI is expressed on the surface of resting B cells and activated T cells, but not resting T cells. TACI interacts with 2 ligands—BAFF (B-cell activating factor), also known as BLys (B-lymphocyte stimulator), which belongs to the TNF family, and APRIL (a proliferation-inducing ligand). The ligands for TACI are expressed on macrophages, monocytes, and dendritic cells. (2) TACI regulates isotype class-switching of immunoglobulins and also is involved in the antibody response to T-independent antigens. (3) TACI is encoded by the TACI gene (official symbol, TNFRSF13B). The human TACI gene locus is located on the short arm of chromosome 17, which is a common target for mutation and rearrangement. (3) The TACI gene consists of 5 exons spanning approximately 35 kb (including 1002 bp upstream of the 5' untranslated region [UTR] and 1024 bp downstream of the 3' UTR). The mRNA length is 1377 bp, encoding for a 294-amino acid protein with a molecular weight of 32.34 kD. In recent studies, 4 mutations (D68X [L69fsX11], C104R, A181E, R202H) have been shown to be statistically significant in common variable immunodeficiency (CVID) and selective IgA deficiency (sIgAD) patients when compared to controls. (4) In addition, several other mutations have been reported but none of these appear to be statistically significant when compared to controls. (4) Two other mutations, P251L and V220A, are considered to be rare polymorphisms as they are present in both controls and patients. (4-6) The TACI gene mutations described so far are nonsense, missense, or frameshift (due to the insertion of a single extra nucleotide) mutations, all of which can be detected by gene sequencing. No large deletions or duplications have been reported for this gene at this time. CVID is a complex, heterogeneous disease with defects in 1 or more of these pathways: B-cell survival; circulating memory B cells (CD27+), including class-switched (CD27+IgM-IgD-), nonswitched (CD27+IgM+IgD+), and IgM-memory B cells (CD27+IgM+IgD-); B-cell activation after receptor cross-linking; T-cell signaling; and cytokine expression. CVID patients have hypogammaglobulinemia with impaired functional antibody responses among other clinical features. While the molecular basis for most cases of CVID and sIgAD remain unknown, a fraction of CVID cases (approximately 20%-25%) have been reported to be associated with mutations in the TACI gene, ICOS, BAFF-R, or CD19. Most cases of CID are sporadic, but at least 10% are familial with a predominance of autosomal dominant over autosomal recessive inheritance. TACI gene mutations account for 8% to 15% of CVID cases depending on the study population and are sporadic in the majority of cases. The familial TACI gene mutations can be inherited in either an autosomal dominant or autosomal recessive fashion. There also appears to be variable penetrance in the familial TACI gene mutations. (7) TACI gene mutations appear to be strongly associated with lymphoproliferative diseases such as splenomegaly or tonsillar hypertrophy. Autoimmune thyroiditis is observed in 15% of TACI gene mutation-positive CVID cases. The incomplete penetrance seen for TACI gene mutations indicates that a mutation can be present, but the individual does not develop the disease phenotype. The known TACI gene mutations appear, in most cases, to be associated with normal protein expression with aberrant or absent functional activity. Consequently, the vast majority (approximately 95%) of cases cannot be identified by the flow cytometry analysis (see IABCS / B-Cell Phenotyping Profile for Immunodeficiency and Immune Competence Assessment, Blood). (7) In <5% of TACI-associated CVID cases, protein expression on B cells is absent, which can be detected by flow cytometry. Therefore, in the presence of a strong clinical indication for CVID and potential TACI gene mutations, such as low to absent IgA levels (in the absence of anti-IgA), lymphoproliferative disease, autoimmune thyroiditis, or...
autoimmune cytopenias, TACI genotyping can determine if mutations are present that could explain the clinical phenotype. Genotyping can also be used to evaluate clinically symptomatic family members of patients with known TACI gene mutations for correlation with clinical phenotype and genetic counseling (TACIG / Transmembrane Activator and CAML Interactor Gene [TACI], Known Mutation Analysis).

**Useful For:** Evaluating individuals with: -Common variable immunodeficiency (CVID) -Clinically symptomatic selective IgA deficiency -Lymphoproliferative disease associated with CVID -Autoimmune phenotypes with CVID These clinical features may be consistent with possible TACI mutations, and the genotyping test is especially useful as a follow-up test when flow cytometry is uninformative. Identification of specific TACI mutations in individuals with abnormal TACI flow cytometry results (from IABCBS / B-Cell Phenotyping Profile for Immunodeficiency and Immune Competence Assessment, Blood).

**Interpretation:** An interpretive report is provided that describes the mutations, if any, their potential clinical significance, and whether they have been previously reported or are new mutations. Variants of unknown clinical significance also will be documented in the report. The published mutations in the TACI gene are a combination of missense, nonsense, small insertion or deletion, and other point mutations, all of which will be detected by full gene sequencing.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:***

**TACIG 89122**

**Transmembrane Activator and CAML Interactor (TACI) Gene, Known Mutation Analysis**

**Clinical Information:** Transmembrane activator and CAML interactor (TACI) is a member of the tumor-necrosis factor (TNF)-like receptor family, a group of receptors that regulate both survival and apoptosis of immune cells.(1) TACI is expressed on the surface of resting B cells and activated T cells, but not resting T cells. TACI interacts with 2 ligands-BAFF (B-cell activating factor), also known as BLys (B-lymphocyte stimulator), which belongs to the TNF family, and APRIL (a proliferation-inducing ligand). The ligands for TACI are expressed on macrophages, monocytes, and dendritic cells.(1) TACI regulates isotype class-switching of immunoglobulins and also is involved in the antibody response to T-independent antigens.(2) TACI is encoded by the TACI gene (official symbol, TNFRSF13B). The human TACI gene locus is located on the short arm of chromosome 17, which is a common target for mutation and rearrangement.(2) The TACI gene consists of 5 exons spanning approximately 35 kb (including 1002 bp upstream of the 5' untranslated region [UTR] and 1024 bp downstream of the 3' UTR). The mRNA length is 1377 bp, encoding for a 294-amino acid protein with a molecular weight of 32.34 kD. Six mutations (D68X [also called L69fsX11], C104R, S144X, A181E, S194X, and R202H) were identified in the TACI gene in the original reports.(3,4) Of these 6 mutations, 4 (D68X, C104R, A181E, and R202H) have been shown to be statistically significant in common variable immunodeficiency (CVID) and selective IgA deficiency patients, when compared to controls.(5) Several other mutations have been reported, but none of these appear to be statistically significant when compared to controls.(5) Two other mutations, P251L and V220A, are considered to be rare polymorphisms as they are present in both controls and patients.(3-5) The TACI gene mutations described so far are nonsense, missense, or frameshift (due to the insertion of a single extra nucleotide) mutations, all of which can be
detected by gene sequencing. No large deletions or duplications have been reported for this gene at this
time. TACI gene mutations account for 8% to 15% of CVID cases depending on the study population and
are sporadic in the majority of cases. The familial TACI gene mutations can be inherited in either an
autosomal dominant or autosomal recessive fashion. There also appears to be variable penetrance in the
familial TACI gene mutations. TACI gene mutations appear to be strongly associated with
lymphoproliferative diseases such as splenomegaly or tonsillar hypertrophy. Autoimmune thyroiditis is
observed in 15% of TACI gene mutation-positive CVID cases. The incomplete penetrance seen for TACI
gene mutations indicates that a mutation can be present, but the individual does not develop the disease
phenotype. The known TACI gene mutations appear, in most cases, to be associated with normal protein
expression with aberrant or absent functional activity and require gene sequencing analysis to confirm the
presence of the mutation as well as correlation with the clinical phenotype.

Useful For: Identifying the presence of a TACI gene mutation in a symptomatic patient when the
mutation has been identified in an affected family member

Interpretation: An interpretive report will be provided that describes the presence or absence of the
previously identified mutations, and their potential clinical significance. Variants of unknown clinical
significance within the specific exon being evaluated also will be documented in the report.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mackay F, Ambrose C: The TNF family members BAFF and APRIL: the
Wilson SA, Garibyan L, et al: TACI is mutant in common variable immunodeficiency and IgA
TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat
coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet

Trazodone (Desyrel)
Reference Values:
Reference Range: 800 - 1600 ng/mL

Tree of Heaven (Ailanthus spp) IgE
Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2
0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“
Reference Values:
<0.35 kU/L

Tree Panel # 1
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
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</tr>
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<tbody>
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<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Tree Panel # 2**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
**Reference Values:**

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<tbody>
<tr>
<td>0</td>
<td>0-0.34</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
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<td>3.50-17.4</td>
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<td>&gt; 100</td>
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Reference values apply to all ages.


---

**TREE3 Panel # 3**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td>Strongly positive Reference values apply to all ages.</td>
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**Trichinella Antibody, Serum**

**Clinical Information:** Trichinosis is an infection by the nematode parasite, Trichinella spiralis. The infection is acquired by ingestion of larvae in inadequately cooked, contaminated meat, especially pork, bear, and walrus meat may also be sources of infection. After ingestion, acid-pepsin digestion in the stomach liberates the larvae, which develop into adult worms in the small intestine. After fertilization, the female worm produces larvae that penetrate the mucosa and seed the skeletal muscles via the bloodstream. In muscle fibers they coil and encyst, remaining viable for up to several years. Diarrhea is the most common symptom associated with intestinal infection with adult worms. Subsequently, during systemic invasion by the larvae, fever, periorbital swelling, muscle pain and swelling, and pulmonary symptoms and rash develop.

**Useful For:** As an adjunct in the diagnosis of trichinosis

**Interpretation:** A positive enzyme-linked immunosorbent assay (ELISA) suggests current infection with Trichinella spiralis. Serology should be used in conjunction with clinical, epidemiologic, and other laboratory tests to establish the correct diagnosis. The number of individuals showing positive results may vary significantly between populations and geographic regions.

**Reference Values:**
Negative (reported as positive or negative)


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**Trichloroacetic Acid, Urine**

**Reference Values:**
Creatinine: >50 mg/dL

Trichloroethane Exposure:
- Normal (unexposed population):
  - None detected
- Exposed:
  - Biological Exposure Index (BEI):
    - 10 mg/L (end of workweek)
  - Toxic:
    - Not established

Trichloroethylene Exposure:
- Normal (unexposed population):
  - None detected
- Exposed:
  - Biological Exposure Index (BEI):
    - 100 mg/g creat (end of workweek)

Biological Tolerance Value (BAT):
- 100 mg/L (end of exposure or end of shift, or after several shifts for long-term exposure)
  - Toxic:
    - Not established

Tetrachloroethylene (Perchloroethylene) Exposure:
- Normal (unexposed population):
  - None detected
- Exposed:
  - Biological Exposure Index (BEI):
7.0 mg/L (end of workweek)
Toxic:
Not established

**FFTRE**

**Trichloroethylene, Occupational Exposure, blood**

**Reference Values:**

- **Free Trichloroethanol Units:** mg/L
  - Normal (Unexposed Population): None Detected
  - Exposed: Biological Exposure Index (BEI): 4.0 mg/L (end of shift at end of workweek)
  - Biological Tolerance Value (BAT): 5.0 mg/L (end of exposure or end of shift, or after several shifts for long term exposure)
  - Toxic: Not established

- **Trichloroethylene Units:** mg/L
  - Normal (unexposed population): None Detected
  - Exposed: Not established
  - Toxic: Greater than 1.5 mg/L

**TRVI**

**Trichoderma viride, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td>1</td>
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<td>Equivocal</td>
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</table>
Trichomonas vaginalis by Nucleic Acid Amplification

**Clinical Information:** Trichomonas vaginalis (TV) is a protozoan parasite that commonly infects the genital tract of men and women. It is now considered to be the most common curable sexually transmitted disease (STD) agent, with an estimated 3.7 million infected individuals in the United States. (1-4) Although up to 70% of infected individuals are asymptomatic, infections may be associated with vaginitis, urethritis, and cervicitis in women, and urethritis and prostatitis in men. (3) Patients that are infected with Trichomonas vaginalis have an increased risk of acquiring other sexually transmitted infections such as HIV, while infections in pregnant women are associated with premature labor, low-birth-weight offspring, premature rupture of membranes, and posthysterectomy/postabortion infection. (3) Symptoms of Trichomonas vaginalis overlap considerably with other sexually transmitted infections and, therefore, laboratory diagnosis is required for definitive diagnosis. The most commonly used method for detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture. (5) Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods. (5) Culture is also technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the APTIMA Trichomonas vaginalis Assay, offer the highest sensitivity and specificity for detection of trichomoniasis. The APTIMA test utilizes target capture, transcription-mediated amplification (TMA), and hybridization protection assay (HPA) technologies for detection of Trichomonas vaginalis ribosomal RNA (rRNA).

**Useful For:** Detection of Trichomonas vaginalis

**Interpretation:** A positive result is considered indicative of current or recent Trichomonas vaginalis infection (trichomoniasis).

**Reference Values:**

<table>
<thead>
<tr>
<th>Reference Values</th>
<th>TVRNA 61755</th>
</tr>
</thead>
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**Clinical References:**

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**Useful For:** Detection of Trichomonas vaginalis

**Interpretation:** A positive result is considered indicative of current or recent Trichomonas vaginalis infection (trichomoniasis).

**Reference Values:**

Negative

**Clinical References:**


**TCPT**

**82720**

**Trichophyton rubrum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td>6</td>
<td>&gt; 100</td>
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Reference values apply to all ages.


**Trichosporon pullulans, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**TWSS**

**Trichrome Water Soluble Stain (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**TGLBF**

**Triglycerides, Body Fluid**

**Clinical Information:** The presence of a chylous effusion, which results from lymphatic drainage into a body cavity, can be determined by identifying triglycerides and chylomicrons in the fluid. Catheter-related iatrogenic effusions can be identified by determining the presence of intravenous solution constituents in the fluid.

**Useful For:** Distinguishing between chylous and nonchylous effusions Determining if bleeding has occurred in a body fluid Identifying iatrogenic effusions

**Interpretation:** Triglyceride concentration >110 mg/dL is highly suggestive of a chylous effusion.

**Reference Values:**
- Not applicable

**Clinical References:** Ellefson RD, Elveback L, Weidman W: Plasma lipoproteins of children and youths in Rochester, MN. DHEW Publication No. (NIH) 1978;78-1472

**TRIGC**

**Triglycerides, CDC, Serum**

**Reference Values:**
- Only orderable as part of a profile. For more information see LMPP / Lipoprotein Metabolism Profile.

**TRIG**

**Triglycerides, Serum**

**Clinical Information:** Triglycerides are esters of the trihydric alcohol glycerol with 3 long-chain fatty acids. They are partly synthesized in the liver and partly derived from the diet. Increased plasma triglyceride levels are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or be associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (eg, prednisone).

**Useful For:** Evaluation of risk factors in individuals with elevated cholesterol values Since cholesterol and triglycerides can vary independently, measurement of both is more meaningful than the measurement of cholesterol only.

**Interpretation:** In the presence of other coronary heart disease risk factors, both borderline-high (150-199 mg/dL) and high values (>200 mg/dL) require attention. Triglyceride concentrations >1,000 mg/dL can lead to abdominal pain and may be life-threatening due to chylomicron-induced pancreatitis.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Non-HDL cholesterol) in adults ages 18 and up:

**TRIGLYCERIDES**
- Normal: <150 mg/dL
- Borderline high: 150-199 mg/dL
- High: 200-499 mg/dL
- Very high: > or =500 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2 to 17:

**TRIGLYCERIDES**
- 2-9 years:
  - Acceptable: <75 mg/dL
  - Borderline high: 75-99 mg/dL
  - High: > or =100 mg/dL
- 10-17 years:
  - Acceptable: <90 mg/dL
  - Borderline high: 90-129 mg/dL
  - High: > or =130 mg/dL

**Clinical References:**

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**FFT3F**

**Triiodothyronine (T3), Free, serum**

**Reference Values:**
2.3 - 5.0 pg/mL

**TMA**

**Trimellitic Anhydride, TMA, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference Values:
Class IgE kU/L Interpretation
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3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


Trimethoprim, Serum

Clinical Information: Trimethoprim is coadministered with sulfamethoxazole for prophylaxis or treatment of bacterial infections. These agents are used to treat a variety of infections including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients such as HIV-positive individuals. Trimethoprim has a wide therapeutic index and dose-dependent toxicity. Trimethoprim accumulates in patients with renal failure. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Accordingly, routine drug monitoring is not indicated in all patients.

Useful For: Monitoring trimethoprim therapy to ensure drug absorption, clearance, or compliance

Interpretation: Most patients will display peak steady state serum concentrations >2.0 mcg/mL when drawn at least 1 hour after an oral dose. Target concentrations may be higher, depending on the intent of therapy.

Reference Values: >2.0 mcg/mL


Trimipramine, Serum

Clinical Information: Trimipramine is a tricyclic antidepressant with additional anxiety-reducing sedative activity. Daily dosages for adults range from 50 mg to 300 mg and are usually divided into 2 to 3 doses per day. Therapeutic ranges are based on serum samples collected at trough (ie, immediately before the next dose). Peak serum concentrations are typically achieved after 1 to 6 hours postdosage. Common
adverse effects include hypotension, tachycardia, constipation, dizziness, somnolence, and blurred vision. Risk of toxicity increases when concentrations >500 ng/mL. Serious adverse effects include coma, seizures, and QRS prolongation with ventricular dysrhythmias.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to trimipramine with serum levels of 150 to 300 ng/mL. Risk of toxicity is increased with trimipramine levels >500 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**
Therapeutic concentration: 150-300 ng/mL
Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

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**TPPTF**

**Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Fibroblasts**

**Clinical Information:** The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. Clinically, they are characterized by vision loss, seizures, mental regression, behavioral changes, movement disorders, and the accumulation of storage material with a characteristic appearance by electron microscopy. Currently, at least 10 genetically distinct NCLs (CLN1-CLN10) are known. The age of onset and rate of deterioration varies according to type of NCL. Tissue damage is selective for the nervous system and many patients die in the first decade of life due to central nervous system degeneration. There is an overall incidence in the United States estimated at 1 in 12,500. Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age of 2. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits (GRODs) in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. Infantile NCL has an incidence of 1 in 20,000 in Finland and is rare elsewhere. The late infantile form of NCL (CLN2) is caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. In addition, molecular genetic testing of CLN1 or CLN2 may allow for identification of the disease causing mutations.

**Useful For:** Evaluation of patients with clinical presentations suggestive of neuronal ceroid lipofuscinoses (NCL) An aid in the differential diagnosis of infantile and late infantile NCL

**Interpretation:** Tripeptidyl peptidase 1 (TPP1) and palmitoyl-protein thioesterase 1 (PPT1) enzyme activity below 5 nmol/h/mg of protein are highly suggestive of late infantile and infantile neuronal ceroid lipofuscinoses, respectively.

**Reference Values:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIPEPTIDYL PEPTIDASE 1</td>
<td>69-934 nmol/h/mg Prot</td>
</tr>
</tbody>
</table>

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Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1965
TPPTL
89494

Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Leukocytes

Clinical Information: The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. Clinically they are characterized by vision loss, seizures, mental regression, behavioral changes, movement disorders, and the accumulation of storage material with a characteristic appearance by electron microscopy. Currently, at least 10 genetically distinct NCLs (CLN1-CLN10) are known. The age of onset and rate of deterioration varies according to type of NCL. Tissue damage is selective for the nervous system and many patients die in the first decade of life due to central nervous system degeneration. There is an overall incidence in the United States estimated at 1 in 12,500. Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age of 2. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits (GRODs) in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. Infantile NCL has an incidence of 1 in 20,000 in Finland and is rare elsewhere. The late infantile form of NCL (CLN2) is caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. In addition, molecular genetic testing of CLN1 or CLN2 may allow for identification of the disease causing mutations.

Useful For: Evaluation of patients with clinical presentations suggestive of neuronal ceroid lipofuscinoses (NCL). An aid in the differential diagnosis of infantile and late infantile NCL.

Interpretation: Tripeptidyl peptidase 1 (TPP1) and palmitoyl-protein thioesterase 1 (PPT1) enzyme activity below 5 nmol/hour/mg of protein are highly suggestive of late-infantile and infantile neuronal ceroid lipofuscinoses, respectively.

Reference Values:
TRIPEPTIDYL PEPTIDASE 1
85-326 nmol/hour/mg protein

PALMITOYL-PROTEIN THIOESTERASE 1
20-93 nmol/hour/mg protein

Trofile Co-Receptor Tropism Assay

**Useful For:** To determine the co-receptor tropism (CCR5, CXCR4, or dual/mixed) of a patient's HIV-1 strain for selection of CCR5 co-receptor antagonist therapy, when a patient's HIV-1 viral load is > or = 1,000 copies/mL.

**Interpretation:** CCR5 Tropic (R5) HIV-1 Virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1 Virus uses CXCR4 to enter CD4+ cells. Dual/Mixed Tropic (D/M) HIV-1 Dual-tropic viruses can use either CCR5 or CXCR4 to enter CD4+ cells. Mixed-tropic populations contain viruses with two or more tropisms. Non-reportable Co-receptor tropism could not be determined by the Trofile assay. Common causes of a non-reportable result are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

Trofile DNA Co-Receptor Tropism Assay

**Useful For:** To determine the co-receptor tropism (CCR5, CXCR4, or dual/mixed) of a patient's HIV-1 strain for selection of CCR5 co-receptor antagonist therapy, when patient's HIV-1 viral load is <1,000 copies/mL.

**Interpretation:** Trofile DNA Viral Classification CCR5 Tropic (R5) HIV-1: Virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1: Virus uses CXCR4 to enter CD4+ cells. Dual/Mixed Tropic (D/M) HIV-1: Dual-tropic viruses can use either CXCR4 or CCR5 to enter CD4+ cells. Mixed-tropic populations contain viruses with 2 or more tropisms. Nonreportable: Co-receptor tropism could not be determined. Common causes of nonreportable results are reduced viral fitness or compromised sample handling. Please note that Trofile DNA sample collection and handling instructions differ from Trofile and other Monogram assays. Trofile uses the complete gp160 coding region of the HIV-1 envelope protein ensuring that all of the determinants of tropism are tested. Subtype is determined based on the HIV-1 gp41 envelope region.

Tropheryma whippelii, Molecular Detection, PCR

**Clinical Information:** Whipple disease is a chronic, systemic illness that in the majority of cases involves the small intestine and its lymphatic drainage. The disease primarily affects middle-aged individuals, with a peak incidence in the third and fourth decades. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple associated bacillus has been difficult because of these limitations. Recently, molecular techniques using PCR and nucleotide sequencing allowed classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whippelii.

**Useful For:** An aid in diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases

**Interpretation:** A positive result strongly suggests a diagnosis of Whipple disease. A negative result does not negate the presence of the organism or active disease, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and/or probes, or the presence of Tropheryma whippelii in quantities less than the limit of detection of the assay.
**WHIPB**
87974

**Tropheryma whipplei, Molecular Detection, PCR, Blood**

**Clinical Information:** Whipple disease is a chronic, systemic illness that in the majority of cases involves the small intestine and its lymphatic drainage. The disease primarily affects middle-aged individuals, with a peak incidence in the third and fourth decades. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease patients reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple-associated bacillus has been difficult because of these limitations. Recently, molecular techniques using PCR and nucleotide sequencing allowed classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

**Useful For:** An aid in diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases

**Interpretation:** A positive result is considered diagnostic of Whipple disease. A negative result does not negate the presence of the organism or active disease, as false negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes or the presence of Tropheryma whipplei in quantities less than the limit of detection of the assay.

**Reference Values:** Not applicable

**Clinical References:**

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**TPNI**
81767

**Troponin I, Serum**

**Clinical Information:** Troponin is a complex that regulates the contraction of striated muscle. It consists of 3 subunits (C, T, and I) that are located periodically along the thin filament of the myofibrils. Troponin I inhibits actomyosin ATPase. Troponin I is an inhibitory protein and exhibits in 3 isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle. The cardiac form of troponin I has 31 amino acid residues on its N-terminal, not present in the skeletal forms, which allow for specific
polyclonal and monoclonal antibody development. The cardiac specificity of this isoform improves the accuracy of diagnosis in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury. Troponin I is the only troponin isotope present in the myocardium and is not expressed during any developmental stage in skeletal muscle. Troponin I is released into the bloodstream within hours of the onset of symptoms of myocardial infarction or ischemic damage. It can be detected at 3 to 6 hours following onset of chest pain with peak concentrations at 12 to 16 hours, and remains elevated for 5 to 9 days.

**Useful For:** Exclusion diagnosis of acute myocardial infarction

**Interpretation:** There are, on occasions, elevations of cardiac troponin T (cTnT) which we use clinically which can be due to skeletal muscle disease. One way to unmask such elevations is to measure cardiac troponin I (cTnI), which will be normal in that circumstance. In addition, at times there are interferences that can cause spurious increases or decreases in cTnT values. Conceptually, these same interferences can occur with cTnI but in any given case, the likelihood of having both assays be confounded in that way is highly unusual. Thus, potential false-positives would be unmasked by a normal cTnI and false-negatives by an elevated value. A reference range study was conducted using the ADVIA Centaur TnI-Ultra assay based on guidance from the Clinical and Laboratory Standards Institute (CLSI) Protocol C28-A2.25. The study, which used 1,845 fresh serum, lithium heparin plasma, and EDTA plasma samples from 648 apparently healthy individuals ranging from 17 to 91 years of age, demonstrated a 99th percentile of 0.04 ng/mL (mcg/L).(1)

**Reference Values:**
- <0.04 ng/mL

**Clinical References:**

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**Troponin T, Serum**

**Clinical Information:** Troponin T is a myofibrillar protein found in striated musculature. There are 2 types of myofilament, a thick filament containing myosin and a thin filament consisting of 3 different proteins: actin, tropomyosin, and troponin. Troponin is itself a complex of 3 protein subunits: troponin T, troponin I, and troponin C. Troponin T binds the troponin complex to tropomyosin. Troponin I inhibits actomyosin ATPase in relation to the calcium concentration. Troponin C, with its 4 binding sites for calcium, mediates calcium dependency. In the cytosol, troponin T is found in both free and protein-bound forms. The unbound (free) pool of troponin T is the source of the troponin T released in the early stages of myocardial damage. Bound troponin T is released from the structural elements at a later stage, corresponding with the degradation of myofibrils that occurs in irreversible myocardial damage. The most common cause of cardiac injury is myocardial ischemia, ie, acute myocardial infarction. Troponin T becomes elevated 2 to 4 hours after the onset of myocardial necrosis, and can remain elevated for up to 14 days. Elevations in troponin T are also seen in patients with unstable angina. The finding of unstable angina and an elevated troponin T are known to have adverse short- and long-term prognoses, as well as a unique beneficial response to an invasive interventional strategy and treatment with the newer antiplatelet agents and low-molecular-weight heparin.

**Useful For:** Exclusion diagnosis of acute myocardial infarction Monitoring acute coronary syndromes and estimating prognosis Possible utility in monitoring patients with nonischemic causes of cardiac injury Troponin T is the cardiac marker of choice for the Mayo Health System for the evaluation of patients with possible cardiovascular injury

**Interpretation:** The upper limit for normal individuals is <0.01 ng/mL (undetectable by this method). For patients who present with acute coronary syndromes, troponin T values > or =0.01 ng/mL that are
rising make the diagnosis of cardiac injury. Decreasing values are indicative of recent cardiac injury. Troponin T values > or =0.01 ng/mL are a prognostic sign in patients with ischemic heart disease and most other situations. Clinical judgment is necessary to distinguish patients who have ischemic heart disease from those who do not. However, all patients with > or =0.01 ng/mL troponin T are at increased risk for cardiac events relative to patients with undetectable troponin T. Patients with low level (<0.20 ng/mL) elevations of troponin T and diagnostic uncertainty for acute coronary syndrome should be evaluated by repeat measurements at 3 and 6 hours including a delta between these time points to determine whether this is an acute or more chronic elevation. However, all patients with > or =0.01 ng/mL troponin T are at increased risk for cardiac events relative to patients with undetectable troponin T.

Reference Values:
<0.01 ng/mL
Values > or =0.01 ng/mL have been shown to have prognostic value.


TROT 82788

Trout, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Trypanosoma cruzi Antibody, IgG, Serum

Clinical Information: Chagas disease (American trypanosomiasis) is an acute and chronic infection caused by the protozoan hemoflagellate, Trypanosoma cruzi, which is endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma, but also has been transmitted by blood transfusion, organ transplantation, and apparently also by food ingestion. The acute febrile infection is most often undiagnosed and often resolves spontaneously. The actively motile (trypomastigote) form may be demonstrated in peripheral blood by stained smears during the acute phase. Chronic infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megesophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of Trypanosoma cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis at this time is made by serology or tissue biopsy. A positive serology is considered presumptive evidence of active infection. Serologically positive asymptomatic persons are capable of transmitting the infection.

Useful For: Diagnosis of Chagas disease (infection with Trypanosoma cruzi)

Interpretation: A positive serology is suggestive of recent infection or past exposure. Results should be correlated with clinical presentation and other laboratory findings. Infected individuals usually begin producing antibodies to Trypanosoma cruzi during the first month following exposure to the parasite. Antibody levels may fluctuate during the chronic phase of the disease and may become undetectable after several months. Uninfected individuals are not expected to have detectable levels of antibodies to Trypanosoma cruzi.

Reference Values:
Negative


Trypanosoma cruzi Antibody, IgM

Reference Values:
Less than 1:16: Negative â€“ No significant level of Trypanosoma cruzi IgM antibody detected

1:16 or greater: Positive â€“ IgM antibodies to Trypanosoma cruzi detected, which may suggest current or recent infection.

Trypsin-Like Immunoreactivity

Reference Values:
Reference Range:
10.0 - 57.0 ng/mL

Expected Cathodic Trypsinogen Concentration Values for the Varied Disease States:
10.0 - 57.0 ng/mL . . . . . . . . . . Healthy Individuals
46.0 ng/mL or less . . . . . . . . . . Chronic Pancreatitis
92.0 - 850.0 ng/mL . . . . . . . . . . Acute Pancreatitis
1.4 ng/mL or less . . . . . . Total Pancreatectomy

Results should be correlated with clinical presentation and other diagnostic data for the diagnosis of pancreatitis.

**TRYPA**

**Tryptase, Autopsy**

**Clinical Information:** Tryptase, a neutral protease, is present within the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes. Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the protryptases reflect the total number of mass cells within the body, but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparin or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of beta-tryptase. After anaphylaxis, mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes. The levels decline under first-order kinetics with a half-life of approximately 2 hours. By comparison, histamine (another immunologic mediator released by activated mast cells) is cleared from blood within minutes. Increased serum levels may also occur after allergen challenge or in patients with systemic mastocytosis or mast cell activation syndrome.

**Useful For:** Assessing mast cell activation, which may occur as a result of anaphylaxis or allergen challenge Assessing patients with systemic mastocytosis or mast cell activation syndrome

**Interpretation:** Increased concentrations of total tryptase may indicate mast cell activation occurring as a result of anaphylaxis or allergen challenge, or it may indicate an increased number of mast cells as seen in patients with mastocytosis. However, no specific cutoff value has been validated for autopsy specimens.

**Reference Values:**
No established reference values


**TRYPT**

**Tryptase, Serum**

**Clinical Information:** Tryptase, a neutral protease, is a dominant protein component of the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes. Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the protryptases reflect the total number of mass cells within the body, but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparin or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of beta-tryptase. After anaphylaxis, mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes. The levels decline under first-order kinetics with a half-life of approximately 2 hours. By comparison, histamine (another immunologic mediator released by activated mast cells) is cleared from blood within minutes. Increased serum levels may also occur after allergen challenge or in patients with systemic mastocytosis or mast cell activation syndrome.

**Useful For:** Assessing mast cell activation, which may occur as a result of anaphylaxis or allergen challenge Assessing patients with systemic mastocytosis or mast cell activation syndrome
**Interpretation:** Levels of total tryptase in serum \( \geq 11.5 \) ng/mL may indicate mast cell activation occurring as a result of anaphylaxis or allergen challenge, or it may indicate increased number of mast cells as seen in patients with mastocytosis.

**Reference Values:**
\(<11.5 \) ng/mL

**Clinical References:**

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**Tryptophan, Plasma**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism have been identified, including glutaric acidemia type 1, which affect other metabolic activities. Amino acid disorders can manifest at any time in a person's life, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Low plasma concentrations of tryptophan have been associated with clinical observations of insomnia, anxiety, and depression. Glutaric acidemia type 1 is an autosomal recessive disorder of tryptophan and lysine metabolism caused by a deficiency of glutaryl-CoA dehydrogenase. Early diagnosis and treatment is essential to help prevent encephalopathic crises leading to brain degeneration. These can be provoked by infections, trauma, fever, and fasting. Treatment consists of preventing neurodegeneration through strict adherence to an emergency protocol. Dietary protein, in particular, lysine, is restricted during the vulnerable period of brain development from 0 to 5 years of age. In addition to other indices of malnutrition, the measurement of plasma concentration of tryptophan is used as an indicator of appropriate dietary therapy.

**Useful For:** Investigating inadequate tryptophan intake and monitoring dietary treatment

**Interpretation:** If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added including a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, if applicable.

**Reference Values:**
\(< \) or \( \leq 23 \) months: 17-75 nmol/mL
2 years-17 years: 23-80 nmol/mL
\( > \) or \( \geq 18 \) years: 29-77 nmol/mL


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**Tryptophan, Urine**

**Clinical Information:** Amino acids are the basic units that make up proteins and are crucial to virtually all metabolic processes in the body. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Hartnup disease is a rare, usually benign, autosomal recessive disorder of renal and intestinal neutral amino acid transport. The clinical features associated with Hartnup disease include an erythematous skin rash on exposed surfaces that is identical to the rash seen in pellagra (niacin deficiency) and cerebral ataxia. Biochemically, it is characterized by increased renal excretion of tryptophan and other neutral amino acids. Newborn screening studies reveal that most affected individuals remain asymptomatic, suggesting that clinical expression of symptoms is dependent on additional genetic or environmental factors (ie, multifactorial disease). Determination of tryptophan by
conventional amino acid profiling methods (ninhydrin-based, HPLC) is hampered by co-elution with other compounds. This liquid chromatography-tandem mass spectrometry method quantifies tryptophan and is interference free.

**Useful For:** Aids in the screening and monitoring of Hartnup disease

**Interpretation:** If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added, including a correlation to available clinical information and recommendations for additional biochemical testing, if applicable.

**Reference Values:**
- ≤35 months: 14-315 nmol/mg creatinine
- 3-8 years: 10-303 nmol/mg creatinine
- 9-17 years: 15-229 nmol/mg creatinine
- ≥18 years: 18-114 nmol/mg creatinine


### ATTRZ 35352

**TTR Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. The most common hereditary amyloidosis is familial transthyretin amyloidosis; an autosomal dominant disorder caused by mutations in the transthyretin (TTR) gene. The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic TTR protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Typically, TTR-associated amyloidosis is progressive over a course of 5 to 15 years and the most common cause of death is cardiomyopathy. Affected individuals may present with a variety of symptoms, including peripheral neuropathy, blindness, cardiomyopathy, nephropathy, autonomic nervous dysfunction, or bowel dysfunction. More than 90 mutations have now been identified within the TTR gene, which cause TTR-associated familial amyloidosis. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of amyloidosis. However, several different mutations have been identified which exhibit considerable clinical overlap. It is important to note that this assay does not detect mutations associated with non-TTR forms of familial amyloidosis. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

**Useful For:** Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

Tubular Reabsorption of Phosphorus, Random

**Clinical Information:** The tubular reabsorption of phosphate (TRP) is the fraction (or percent) of filtered phosphorus that is reabsorbed by renal tubules. Its measurement is useful when evaluating patients with hypophosphatemia. In general, a reduced TRP in the presence of hypophosphatemia is indicative of a renal defect in phosphate reabsorption. The ratio of the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate (TmP/GFR) is considered the most convenient way to evaluate renal phosphate transport and is referred to as the theoretical renal phosphate threshold. This corresponds to the theoretical lower limit of plasma phosphate below which all filtered phosphate would be reabsorbed. Although direct measurements of parathyroid hormone (PTH), which increases renal phosphate excretion, have replaced much of the utility of TmP/GFR measurements, it may still be useful in assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia.

**Useful For:** Assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia including hypophosphatemic rickets, tumor-induced osteomalacia and tumoral calcinosis Adjusting phosphate replacement therapy in severe deficiency states monitoring the renal tubular recovery from acquired Fanconi's syndrome

**Interpretation:** Interpretation of tubular reabsorption of phosphate (TRP) and TmP/GFR is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration. TmP/glomerular filtration rate (GFR) is independent of dietary phosphorus intake, tissue release of phosphorus, and GFR.

**Reference Values:**

**TUBULAR REABSORPTION OF PHOSPHORUS**

>80%

(Although, tubular reabsorption of phosphorus levels must be interpreted in light of the prevailing plasma phosphorus and glomerular filtration rate.)

**TUBULAR MAXIMUM PHOSPHORUS REABSORPTION/GLOMERULAR FILTRATION RATE (TmP/GFR)**

2.6-4.4 mg/dL (0.80-1.35 mmol/L)

**PHOSPHORUS (INORGANIC)**

**Males**

1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are <12 months of age.

**Females**

1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are <12 months of age.

**CREATININE**

**Males**

12-24 months: 0.1-0.4 mg/dL
3-4 years: 0.1-0.5 mg/dL
5-9 years: 0.2-0.6 mg/dL  
10-11 years: 0.3-0.7 mg/dL  
12-13 years: 0.4-0.8 mg/dL  
14-15 years: 0.5-0.9 mg/dL  
> or =16 years: 0.8-1.3 mg/dL  
Reference values have not been established for patients that are <12 months of age.  

Females  
12-36 months: 0.1-0.4 mg/dL  
4-5 years: 0.2-0.5 mg/dL  
6-8 years: 0.3-0.6 mg/dL  
9-15 years: 0.4-0.7 mg/dL  
> or =16 years: 0.6-1.1 mg/dL  
Reference values have not been established for patients that are <12 months of age.

**Clinical References:**  

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**Tumor Necrosis Factor-Alpha, Highly Sensitive**

**Reference Values:**

TNF-Alpha, Highly Sensitive 1.2 – 15.3 pg/mL

TNF-alpha is not to be used as a diagnostic procedure without confirmation of the diagnosis by another established product or procedure.

The reference range is intended to be used for blood samples only. Reference ranges for body fluids other than blood have not been established.

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**Tuna, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivitiy (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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### Turkey Feathers, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>5</td>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>
Turkey IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Turkey, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**FCTUR**

**Turmeric (Curcuma longa) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**TBLU**

**Turnbull Blue, Nrv ST**

**Reference Values:**
Report sent under separate cover.

**TRYPI**

**Tyrophagus putrescentiae, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 199

FSABI 58004

Tysabri (Natalizumab) Immunogenicity

Reference Values:
Negative

UBE3Z 35565

UBE3A Gene, Full Gene Analysis

Clinical Information: Angelman syndrome (AS) is characterized by significant developmental delay and mental retardation, ataxia, jerky arm movements, unprovoked laughter, seizures, and virtual absence of speech. AS has several known genetic causes. About 65% to 80% of affected individuals have a de novo deletion of essentially the same region of chromosome 15 detected for Prader-Willi syndrome (PWS): 15q11.2-13. The deletion can often be identified by high-resolution chromosome analysis in conjunction with FISH analysis. Molecular testing has shown that the AS deletion occurs only on the copy of chromosome 15 inherited from the mother. In about 5% of patients with AS, the affected individuals have inherited 2 copies of chromosome 15 from their father (paternal uniparental disomy) and no copies of chromosome 15 from their mother. Thus, the individuals with AS resulting from deletion or uniparental disomy are deficient for maternally derived genes from chromosomes 15. Deletions and uniparental disomy occur as de novo events during conception, so the recurrence risk to siblings is very low. Both of these genetic alterations, along with imprinting center defects (accounting for another 2%-5% of AS cases), cause an abnormal methylation pattern in the PWS/AS region of chromosome 15. Another 10% of patients with AS have a documented mutation in the UBE3A gene located in the PW/AS region on chromosome 15. Mutations can either be maternally inherited in an autosomal dominant fashion or de novo. If the mutation is inherited, the risk to all future pregnancies is 50%. If testing of the affected individual's mother confirms she does not carry the mutation, the risk to future pregnancies is low but not zero, as cases of germline mosaicism have been reported. Individuals with a UBE3A mutation will display a normal methylation pattern. No chromosomal or DNA abnormality has been identified in the remainder of clinically diagnosed AS patients (15%-25%). These patients may have genetic alterations that cannot be detected by current testing methods or alterations in as yet unidentified genes. Initial studies to rule-out AS should include high-resolution cytogenetic analysis (CMS / Chromosome Analysis, for Congenital Disorders, Blood) to identify chromosome abnormalities that may have phenotypic overlap with AS, and methylation-sensitive, multiple ligation-dependent probe amplification (PWAS / Prader-Willi/Angelman Syndrome, Molecular Analysis) to identify deletions, duplications, and methylation defects. In cases where methylation analysis is negative, sequencing of the UBE3A gene may provide additional diagnostic information.

Useful For: Confirmation of a diagnosis of Angelman syndrome in patients who have previously tested negative by methylation analysis

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

GALE

UDP-Galactose 4' Epimerase (GALE), Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared to intermediate epimerase deficiency galactosemia which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and renal dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of renal and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, females with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6,700 in African American infants to 1 in 70,000 infants of European ancestry. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency. The quantitative measurement of Gal-1-P (GAL1P / Galactose-1-Phosphate (Gal-1-P), Erythrocytes) is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are normal, but an infant has an elevated Gal-1-P, then epimerase deficiency galactosemia is to be considered. Molecular testing via sequencing of the GALE gene may be performed. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Diagnosis of UDP-galactose 4' epimerase deficiency

Interpretation: An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information. For galactokinase deficiency, see GALK / Galactokinase, Blood. For galactose-1-phosphate uridyltransferase deficiency, see GALT / Galactose-1-Phosphate Uridyltransferase, Blood.

Reference Values:
>5.0 nmol/h/mg of hemoglobin

UDP-Glucuronosyl Transferase 1A1 (UGT1A1) Gene, Known Mutation

**Clinical Information:** Excess levels of bilirubin, which is a by-product of heme, have been associated with deleterious health effects. Uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) is responsible for bilirubin conjugation with glucuronic acid. This renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine.(1) Genetic variants in the UGT1A1 gene may cause reduced or absent UGT1A1 enzymatic activity resulting in hyperbilirubinemia. Gilbert syndrome, found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL).(2) Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Crigler-Najjar (CN) syndrome types I and II are inherited causes of severe unconjugated hyperbilirubinemia. CN type I is associated with the complete absence of UGT1A1 activity and usually presents as intense jaundice in the first days of life and persists thereafter.(3) CN type II is a milder form of hyperbilirubinemia, as compared to CN type I, with at least partial UGT1A1 activity. Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN type II; CN type I does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause kernicterus, which is bilirubin-induced brain damage. In addition to phenobarbital, treatments of CN may include: phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation. The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. This test is intended for analysis of a specific UGT1A1 gene variant or variants that have already been identified in an affected family member. Analysis is performed for the familial variants only.

**Useful For:** Identifying the presence of a UGT1A1 variant when the variant has been previously identified in a family member (carrier or affected)

**Interpretation:** An interpretive report will be provided. UGT1A1 is a pharmacogene and patients with reduced UGT1A1 enzyme activity are at risk for adverse outcomes with certain drugs. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 alleles associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Mutation, Saliva

Clinical Information: Excess levels of bilirubin, which is a by-product of heme, have been associated with deleterious health effects. Uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) is responsible for bilirubin conjugation with glucuronic acid. This renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. (1) Genetic variants in the UGT1A1 gene may cause reduced or absent UGT1A1 enzymatic activity resulting in hyperbilirubinemia. Gilbert syndrome, found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). (2) Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Crigler-Najjar (CN) syndrome types I and II are inherited causes of severe unconjugated hyperbilirubinemia. CN type I is associated with the complete absence of UGT1A1 activity and usually presents as intense jaundice in the first days of life and persists thereafter. (3) Type II is a milder form of hyperbilirubinemia, as compared to CN type I, with at least partial UGT1A1 activity. Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN type II; CN type I does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause kernicterus, which is bilirubin-induced brain damage. In addition to phenobarbital, treatments of CN may include: phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation. The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. This test is intended for analysis of a specific UGT1A1 gene variant or variants that have already been identified in an affected family member. Analysis is performed for the familial variants only.

Useful For: Identifying the presence of a UGT1A1 variant when the variant has been previously identified in a family member (carrier or affected) Genotyping patients who prefer not to have venipuncture done

Interpretation: An interpretive report will be provided. UGT1A1 is a pharmacogene and patients with reduced UGT1A1 enzyme activity are at risk for adverse outcomes with certain drugs. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 alleles associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice).

Reference Values: An interpretive report will be provided.


UDP-Glucuronosyl Transferase 1A1 (UGT1A1), Full Gene Sequencing, Hyperbilirubinemia

Clinical Information: Excess levels of bilirubin, which is a by-product of heme, have been associated with deleterious health effects. Uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) is responsible for bilirubin conjugation with glucuronic acid. This renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. (1) Genetic variants in UGT1A1 may cause reduced or absent UGT1A1 enzymatic activity resulting in hyperbilirubinemia. Gilbert syndrome, found in 5% to 10% of the population, is the most common hereditary cause of
increased bilirubin and is associated with mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL).(2) Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Crigler-Najjar (CN) syndrome types I and II are inherited causes of severe unconjugated hyperbilirubinemia. CN type I is associated with the complete absence of UGT1A1 activity and usually presents as intense jaundice in the first days of life and persists thereafter.(3) CN type II is a milder form of hyperbilirubinemia, as compared to CN type I, with at least partial UGT1A1 activity. Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN type II; CN type I does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause kernicterus, which is bilirubin-induced brain damage. In addition to phenobarbital, treatments of CN may include: phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation. The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. In this assay, the promoter, exons, exon-intron boundaries, and a region in the distal promoter called the "phenobarbital response enhancer module," which is associated with transcriptional activity of the gene, are assessed for variants.(4)

**Useful For:** Identifying individuals who are at risk of hyperbilirubinemia Confirmation of a diagnosis of Gilbert or Crigler-Najjar syndromes Verification of carrier status for Gilbert or Crigler-Najjar syndromes

**Interpretation:** An interpretive report is provided. UGT1A1 is a pharmacogene and patients with reduced UGT1A1 enzyme activity are at risk for adverse outcomes with certain drugs. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 alleles associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**UDP-Glucuronosyl Transferase 1A1 (UGT1A1), Full Gene Sequencing, Hyperbilirubinemia, Saliva**

**Clinical Information:** Excess levels of bilirubin, which is a by-product of heme, have been associated with deleterious health effects. Uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) is responsible for bilirubin conjugation with glucuronic acid. This renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine.(1) Genetic variants in the UGT1A1 gene may cause reduced or absent UGT1A1 enzymatic activity resulting in hyperbilirubinemia. Gilbert syndrome, found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL).(2) Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Crigler-Najjar (CN) syndrome types I and II are inherited causes of severe unconjugated hyperbilirubinemia. CN type I is associated with the complete absence of UGT1A1 activity and usually presents as intense jaundice in the first days of life and persists thereafter.(3) CN type II is a milder form of hyperbilirubinemia, as compared to CN type I, with at least partial UGT1A1 activity. Phenobarbital, a
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**Useful For:** Identifying individuals who are at risk of hyperbilirubinemia Confirmation of a diagnosis of Gilbert or Crigler-Najjar syndromes Verification of carrier status for Gilbert or Crigler-Najjar syndromes Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report is provided. UGT1A1 is a pharmacogene and patients with reduced UGT1A1 enzyme activity are at risk for adverse outcomes with certain drugs. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 alleles associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**UGTI**

**UDP-Glucuronosyl Transferase 1A1 (UGT1A1), Full Gene Sequencing, Irinotecan Hypersensitivity**

**Clinical Information:** Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), is responsible for bilirubin conjugation with glucuronic acid. This renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine.(1) UGT1A1 is involved in the metabolism of irinotecan, a topoisomerase I inhibitor. Irinotecan is a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. It is a produg that forms an active metabolite, SN-38. SN-38 is normally inactivated by conjugation with glucuronic acid followed by biliary excretion into the gastrointestinal tract. If UGT1A1 activity is impaired or deficient due to mutations in the coding region or promoter TA (thymine, adenine) repeat polymorphisms, SN-38 fails to become conjugated with glucuronic acid, increasing the concentration of SN-38. This can result in severe neutropenia. The combination of neutropenia with diarrhea can be life-threatening.(2,3) Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 alleles associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice). The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. The
promoter, exons, exon-intron boundaries, and a region in the distal promoter called the "phenobarbital response enhancer module," which is associated with transcriptional activity of the gene, are assessed for variants in this assay.(4)

**Useful For:** Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1, including irinotecan, atazanavir, nilotinib, pazopanib, and belinostat

**Interpretation:** An interpretive report will be provided. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**UDP-Glucuronosyl Transferase 1A1 (UGT1A1), Full Gene Sequencing, Irinotecan Hypersensitivity, Saliva

**Clinical Information:** Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), is responsible for bilirubin conjugation with glucuronic acid. This renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine.(1) UGT1A1 is involved in the metabolism of irinotecan, a topoisomerase I inhibitor. Irinotecan is a chemotherapeutic drug used to treat solid tumors including colon, rectal, and lung cancers. It is a produg that forms an active metabolite, SN-38. SN-38 is normally inactivated by conjugation with glucuronic acid followed by biliary excretion into the gastrointestinal tract. If UGT1A1 activity is impaired or deficient due to mutations in the coding region or promoter TA (thymine, adenine) repeat polymorphisms, SN-38 fails to become conjugated with glucuronic acid, increasing the concentration of SN-38. This can result in severe neutropenia. The combination of neutropenia with diarrhea can be life-threatening.(2,3) Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 alleles associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice). The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. The
promoter, exons, exon-intron boundaries, and a region in the distal promoter called the "phenobarbital response enhancer module," which is associated with transcriptional activity of the gene, are assessed for variants in this assay.(4)

Useful For: Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1, including irinotecan, atazanavir, nilotinib, pazopanib, and belinostat.

Genotyping patients who prefer not to have venipuncture done

Interpretation: An interpretive report will be provided. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.


UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, UGT1A1

Clinical Information: Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP)-glycuronosyl transferase 1A1 (UGT1A1), is responsible for phase II conjugation of certain drugs, like irinotecan. UGT1A1 is additionally responsible for glucuronide conjugation of bilirubin, which renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. Reduced UGT1A1 gene transcription due to variation in the number of thymine-adenine (TA) repeats in the TATA box of the gene promoter results in reduced enzymatic activity and an increased risk for adverse outcomes in response to drugs metabolized by UGT1A1. Such TA repeat variants are also associated with Gilbert syndrome (unconjugated hyperbilirubinemia). The TA repeat number may vary from 5 to 8 TA repeats, with 6 TA repeats being the most common allele (considered the normal allele), resulting in normal UGT1A1 expression. In addition, the rare 5 TA repeat (TA5 or *36: c.-41_-40delTA) has normal UGT1A1 expression. Individuals with 7 TA repeats (TA7 or *28: c.-41_-40dupTA) or the rare 8 TA repeats (TA8 or *37: c.-43_-40dupTATA) have decreased expression of UGT1A1. Approximately 10% to 15% of Caucasians and African Americans are homozygous for the TA7 repeat (*28/*28). UGT1A1 is involved in the metabolism of irinotecan, a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. If UGT1A1 activity is reduced or deficient, the active irinotecan metabolite (SN-38) is less
efficiently conjugated with glucuronic acid, which leads to an increased concentration of SN-38. This in turn can result in severe neutropenia; and the combination of neutropenia with diarrhea can be life-threatening. Individuals who are homozygous for *28 (TA7) have a 50% higher risk of experiencing severe (grade 4 or 5) neutropenia following the administration of irinotecan. Approximately 40% of individuals treated with irinotecan are heterozygous for the TA7 repeat allele (ie, TA6/TA7 or heterozygous *28). These individuals are also at increased risk of grade 4 neutropenia. The drug label for irinotecan indicates that individuals homozygous or heterozygous for TA repeat variants have a higher risk for severe or life-threatening neutropenia. The risk is thought to be greatest in individuals who receive irinotecan once every 3 weeks. Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have reduced activity alleles. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment that indicate patients who are homozygous for a reduced activity (decreased expression) allele should be considered for an alternate medication due to the significant risk for developing hyperbilirubinemia (jaundice). Gilbert syndrome (GS), found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with usually benign, mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Homozygosity for the reduced activity alleles, TA7 and TA8, or compound heterozygosity (TA7/TA8) is consistent with a diagnosis of Gilbert syndrome. Heterozygosity for TA7 or TA8 is consistent with carrier status for Gilbert syndrome.

Useful For: Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1; especially irinotecan, but also including nilotinib, pazopanib, and belinostat
Identifying individuals with Gilbert syndrome due to the presence of homozygous TA7, homozygous TA8, or compound heterozygous TA7/TA8 Identifying individuals who are carriers of Gilbert syndrome due to the presence of heterozygous TA7 or TA8

Interpretation: An interpretive report will be provided. Drug-drug interactions must be considered when predicting the UGT1A1 phenotype, especially in individuals heterozygous for the TA7 polymorphism (see Cautions). For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

enzymes, uridine diphosphate-glycuronosyl transferase 1A1 (UGT1A1), is responsible for phase II conjugation of certain drugs, like irinotecan. UGT1A1 is additionally responsible for glucuronide conjugation of bilirubin, which renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. Reduced UGT1A gene transcription due to variation in the number of thymine-adenine (TA) repeats in the TATA box of the gene promoter results in reduced enzymatic activity and an increased risk for adverse outcomes in response to drugs metabolized by UGT1A1. Such TA repeat variants are also associated with Gilbert syndrome (unconjugated hyperbilirubinemia). The TA repeat number may vary from 5 to 8 TA repeats, with 6 TA repeats being the most common allele (considered the normal allele), resulting in normal UGT1A1 expression. In addition, the rare 5 TA repeat (TA5 or *36: c.-41_-40delTA) has normal UGT1A1 expression. Individuals with 7 TA repeats (TA7 or *28: c.-41_-40dupTA) or the rare 8 TA repeats (TA8 or *37: c.-43_-40dupTATA) have decreased expression of UGT1A1. Approximately 10% to 15% of Caucasians and African Americans are homozygous for the TA7 repeat (*28/*28). UGT1A1 is involved in the metabolism of irinotecan, a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. If UGT1A1 activity is reduced or deficient, the active irinotecan metabolite (SN-38) is less efficiently conjugated with glucuronic acid, which leads to an increased concentration of SN-38. This in turn can result in severe neutropenia; and the combination of neutropenia with diarrhea can be life-threatening. Individuals who are homozygous for *28 (TA7) have a 50% higher risk of experiencing severe (grade 4 or 5) neutropenia following the administration of irinotecan. Approximately 40% of individuals treated with irinotecan are heterozygous for the TA7 polymorphism (TA6/TA7 or heterozygous *28). These individuals are also at increased risk of grade 4 neutropenia. The drug label for irinotecan indicates that individuals homozygous or heterozygous for TA repeat variants have a higher risk for severe or life-threatening neutropenia. The risk is thought to be greatest in individuals who receive irinotecan once every 3 weeks. Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have reduced activity alleles. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment that indicate patients who are homozygous for a reduced activity (decreased expression) allele should be considered for an alternate medication due to the significant risk for developing hyperbilirubinemia (jaundice). Gilbert syndrome (GS), found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with usually benign, mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Homozygosity for the reduced activity alleles, TA7 and TA8, or compound heterozygosity (TA7/TA8) is consistent with a diagnosis of Gilbert syndrome. Heterozygosity for TA7 or TA8 is consistent with carrier status for Gilbert syndrome.

**Useful For:** Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1; especially irinotecan, but also including nilotinib, pazopanib, and belinostat. Identifying individuals with Gilbert syndrome due to the presence of homozygous TA7, homozygous TA8, or compound heterozygous TA7/TA8. Identifying individuals who are carriers of Gilbert syndrome due to the presence of heterozygous TA7 or TA8. Genotyping patients who prefer not to have venipuncture done.

**Interpretation:** An interpretive report will be provided. Drug-drug interactions must be considered when predicting the UGT1A1 phenotype, especially in individuals heterozygous for the TA7 polymorphism (see Cautions). For additional information regarding pharmacogenomic genes and their associated drugs, please see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Ulocladium chartarum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*apply to all ages.*

occurs during the formation of egg or sperm cells (meiosis). When an error causing UPD occurs during meiosis I both chromosome homologs from a single parent are transmitted, and heterodisomy results. When the error causing UPD occurs during meiosis II or as a postzygotic event, and a single parental homolog is transmitted to offspring in duplicate, isodisomy results. Meiotic recombination events within the context of UPD often result in a mixture of heterodisomy and isodisomy. UPD can involve an entire chromosome or only a segment. Mosaicism for UPD also occurs in combination with either chromosomally normal or abnormal cell lines. When UPD occurs, the imbalance of maternal versus paternal genetic information for the involved chromosome can be associated with clinical symptoms in the affected child. UPD does not always impart an abnormal clinical phenotype however. In fact, while isodisomy can result in disease due to a recessive allele at any location, heterodisomy is not expected to result in an abnormal clinical phenotype unless the involved chromosome or chromosomal segment includes imprinted genes. Imprinted genes demonstrate differential expression depending on parent of origin. Disorders that result from UPD of imprinted genes are not due to a defect in the imprinting mechanism itself, but rather they are due to an unbalanced parental contribution of normally imprinted alleles that results in altered expression of imprinted genes. For example, when maternal UPD 15 occurs (2 copies of the maternal chromosome 15 instead of 1 maternal and 1 paternal copy of chromosome 15), it causes Prader-Willi syndrome due to the lack of paternally expressed genes at the imprinted site. UPD has been described for many but not all chromosomes. In addition to the rare cases of autosomal recessive disease that result from isodisomy, clinical syndromes associated with UPD have been described for only a few chromosomes, including Russell-Silver syndrome (UPD 7), Prader-Willi syndrome (UPD 15), Angelman syndrome (UPD 15), transient neonatal diabetes (UPD 6), and UPD of chromosome 14. UPD cannot be identified by gross cytogenetic analysis and requires DNA-based analysis using multiple polymorphic markers spanning the chromosome of interest. Specimens from both parents and the child or fetus are required.

**Useful For:** Evaluation of patients presenting with mosaicism, confined placental mosaicism, or Robertsonian translocations Evaluation of patients presenting with features of disorders known to be associated with uniparental disomy (eg, Russell-Silver syndrome) Evaluation of disease mechanism in individuals with rare autosomal recessive disease and only one carrier parent

**Interpretation:** An interpretative report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### UNHB 9095

**Unstable Hemoglobin, Blood**

**Clinical Information:** Unstable hemoglobin disease is rare and may be caused by any 1 of a large number of hemoglobin variants. They are inherited as an autosomal dominant trait. The severity of the disease varies according to the hemoglobin variant; there may be no clinical symptoms or the disease may produce a mild, moderate, or severe hemolytic anemia. The stained peripheral blood smear shows anisocytosis, poikilocytosis, basophilic stippling, polychromasia and, sometimes, hypochromia. The reticulocyte count may be increased. Splenomegaly and Heinz bodies may also be present.

**Useful For:** Work-up of congenital hemolytic anemias

**Interpretation:** An abnormal or unstable result is indicative of a hemoglobin variant present. Other confirmatory tests should be performed to identify the hemoglobinopathy (HBELC / Hemoglobin Electrophoresis Cascade, Blood).

**Reference Values:**
Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Only orderable as part of a profile or as a reflex. For more information see HAEVP / Hemolytic Anemia Evaluation; or HBELC / Hemoglobin Electrophoresis Cascade, Blood; or THEVP / Thalassemia and Hemoglobinopathy Evaluation; or REVE / Erthrocytosis Evaluation; or MEVP / Methemoglobinemia Evaluation.

Normal (reported as normal [stable] or abnormal [unstable])


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**FURA 90316**  
**Uranium, Urine**

**Reference Values:**  
Reporting limit determined each analysis

Normally: Less than 0.1 mcg/L

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**URAU 8330**  
**Urea, 24 Hour, Urine**

**Clinical Information:** Urea is a low molecular weight substance (Mol. Wt.=60) that is freely filtered by glomeruli and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors which tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors which reduce urea excretion include low protein intake and conditions which result in low urine output (eg, dehydration).

**Useful For:** Assessment of protein intake and/or nitrogen balance

**Interpretation:** Because multiple factors (glomerular filtration rate, dietary protein intake, protein catabolic rate, hydration state, etc.) can independently affect the urinary excretion of urea, all of these factors must be taken into account when interpreting the results.

**Reference Values:**

10-35 g/24 hours


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**RURAU 89845**  
**Urea, Random, Urine**

**Clinical Information:** Urea is a low molecular weight substance (Mol Wt=60) that is freely filtered by glomeruli and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors that tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors that reduce urea excretion include low protein intake and conditions which result in low urine output (eg, dehydration). Urea excretion is a useful marker of protein metabolism. In oliguric patients with a rising creatinine a fractional excretion of urea <35% is consistent with a prerenal cause, while values >35% are more consistent with acute kidney injury. The fractional excretion of sodium is also used for this purpose, but may be more affected by diuretics. Therefore, the fractional excretion of urea may be particularly useful for patients receiving diuretics.
Useful For: Assessment of renal failure (prerenal vs acute kidney injury)

Interpretation: Fractional excretion of urea <35% is consistent with a prerenal cause.

Reference Values:
No established reference values

Clinical References:

Ureaplasma species, Molecular Detection, PCR

Clinical Information: Ureaplasma urealyticum and Ureaplasma parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. Ureaplasma urealyticum and Ureaplasma parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and they have been associated with infected renal stones. Ureaplasma urealyticum and Ureaplasma parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningoencephalitis and pneumonia. In addition, Ureaplasma urealyticum and Ureaplasma parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, Ureaplasma urealyticum and Ureaplasma parvum have been found to cause hyperammonemia in lung transplant recipients.(1) In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although Ureaplasma urealyticum and Ureaplasma parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. PCR detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of Ureaplasma urealyticum and Ureaplasma parvum, which is not easily accomplished with culture. PCR assay has replaced conventional culture for Ureaplasma urealyticum and Ureaplasma parvum at Mayo Medical Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and Ureaplasma parvum from genitourinary, reproductive, bone and joint, and lower respiratory sources

Interpretation: A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and Ureaplasma parvum ureC gene indicates the presence of Ureaplasma urealyticum or Ureaplasma parvum DNA in the specimen. A negative PCR result indicates the absence of detectable Ureaplasma urealyticum and Ureaplasma parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Ureaplasma urealyticum or Ureaplasma parvum in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References:
**Uric Acid, 24 Hour, Urine**

**Clinical Information:** Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and also endogenous nucleic acid breakdown.

**Useful For:** Assessment and management of patients with kidney stones, particularly uric acid stones

**Interpretation:** Urinary uric acid excretion is elevated in a significant proportion of patients with uric acid stones. Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins.

**Reference Values:**
Diet-dependent: <750 mg/24 hours

The reference value is for a 24-hour collection. Specimens collected for other than a 24-hour time period are reported in unit of mg/dL, for which reference values are not established.


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**Uric Acid, Body Fluid**

**Reference Values:**
Units: mg/dL

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**Uric Acid, Random, Urine**

**Clinical Information:** Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and also endogenous nucleic acid breakdown. Acute uric acid nephropathy can cause acute renal failure due to uric acid precipitation within tubules. This is most commonly seen in patients with hemalogic malignancies (eg, lymphoma, leukemia), often after acute lysis of cells by chemotherapy. Less commonly this may be seen with seizures, treatment of solid tumors, overproduction of uric acid in metabolic disorders such as Lesch-Nyhan syndrome or decreased uric acid reabsorption in the proximal nephron due to tubular disorder (Fanconi syndrome).

**Useful For:** Differentiation of acute uric acid nephropathy from other causes of acute renal failure

Patients who cannot collect a 24-hour specimen, typically small children, a uric acid creatinine ratio can be used to approximate 24-hour excretion

**Interpretation:** Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins. A uric acid to creatinine ratio (mg/mg) >1.0 is consistent with acute uric acid nephropathy, whereas values <0.75 are consistent with other causes of acute renal failure. A timed 24-hour collection is usually the preferred method for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of clinical use in 2 scenarios, however: -When acute renal failure secondary to uric acid is suspected, a uric acid to creatinine ratio (mg/mg) >1.0 is consistent with acute uric acid nephropathy, whereas values <0.75 are consistent with other causes of acute renal failure. -In patients who cannot collect a 24-hour specimen, typically small children, a uric acid creatinine ratio can be used to approximate 24-hour excretion
excretion. Pediatric Reference Ranges of Uric Acid/Creatinine (mg/mg) Age (year) 5th Percentile 95th Percentile 0-0.5 >1.189 <2.378 0.5-1 >0.40 <2.743 1-2 >0.21 <2.080 2-3 >0.20 <0.968 >3-5 >0.19 <0.594 <1.635 >1.189 7-10 >0.46 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594 Matos V, Van Melle G, Werner D et al: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis 1999;34:e1

Reference Values:
No established reference values


Uric Acid, Serum

Clinical Information: Uric acid is the final product of purine metabolism in humans. Purines, compounds that are vital components of nucleic acids and coenzymes, may be synthesized in the body or they may be obtained by ingesting foods rich in nucleic material (eg, liver, sweetbreads). Approximately 75% of the uric acid excreted is lost in the urine; most of the remainder is secreted into the gastrointestinal tract, where it is degraded to allantoin and other compounds by bacterial enzymes. Asymptomatic hyperuricemia is frequently detected through biochemical screening. The major causes of hyperuricemia are increased purine synthesis, inherited metabolic disorder, excess dietary purine intake, increased nucleic acid turnover, malignancy, cytotoxic drugs, and decreased excretion due to chronic renal failure or increased renal reabsorption. Long-term follow-up of these patients is undertaken because many are at risk of developing renal disease; few of these patients ever develop the clinical syndrome of gout. Hypouricemia, often defined as serum urate <2.0 mg/dL, is much less common than hyperuricemia. It may be secondary to severe hepatocellular disease with reduced purine synthesis, defective renal tubular reabsorption, overtreatment of hyperuricemia with allopurinol, as well as some cancer therapies (eg, 6-mercaptopurine).

Useful For: Diagnosis and treatment of renal failure and monitoring patients receiving cytotoxic drugs and a variety of other disorders, including gout, leukemia, psoriasis, starvation and other wasting conditions

Interpretation: Hyperuricemia is most commonly defined by serum or plasma uric acid concentrations >8.0 mg/dL in males or >6.1 mg/dL in females.

Reference Values:
Males
1-10 years: 2.4-5.4 mg/dL
11 years: 2.7-5.9 mg/dL
12 years: 3.1-6.4 mg/dL
13 years: 3.4-6.9 mg/dL
14 years: 3.7-7.4 mg/dL
15 years: 4.0-7.8 mg/dL
> or =16 years: 3.7-8.0 mg/dL
Reference values have not been established for patients who are <12 months of age.

Females
1 year: 2.1-4.9 mg/dL
2 years: 2.1-5.0 mg/dL
3 years: 2.2-5.1 mg/dL
4 years: 2.3-5.2 mg/dL
5 years: 2.3-5.3 mg/dL
6 years: 2.3-5.4 mg/dL
7-8 years: 2.3-5.5 mg/dL
9-10 years: 2.3-5.7 mg/dL

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLabs.com
11 years: 2.3-5.8 mg/dL
12 years: 2.3-5.9 mg/dL
> or =13 years: 2.7-6.1 mg/dL
Reference values have not been established for patients who are <12 months of age.


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**Urinalysis, Complete, Includes Microscopic**

**Clinical Information:** The kidney plays a key role in the excretion of by-products of cellular metabolism and regulation of water, acid-base, and electrolyte balance. Urine is produced by filtration of plasma in the renal glomeruli, followed by tubular secretion and/or reabsorption of water and other compounds. Abnormalities detected by urinalysis may reflect either urinary tract diseases (eg, infection, glomerulonephritis, loss of concentrating capacity) or extrarenal disease processes (eg, glucosuria in diabetes, proteinuria in monoclonal gammopathies, bilirubinuria in liver disease).

**Useful For:** Screening for urinary tract diseases and some nonrenal diseases

**Interpretation:** Osmolality: Osmolality is an index of the solute concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality. In a random urine specimen, a protein/creatinine or protein/osmolality ratio can be used to roughly approximate 24-hour excretion rates. The normal protein-to-creatine ratio for males 18 to 83 years is <011 mg/mg creatinine and for females 18 to 83 years is <0.16 mg/mg creatinine. The normal protein-to-osmolality ratio is <0.27.(1) For patients <18 years of age and >83 years of age no reference range has been established. Reference values for osmolality: 0-12 months: 50-750 mOsm/kg; >12 months: 150-1,150 mOsm/kg -Please note above the age of 20 there is an age-dependent decline in the upper reference range of approximately 5 mOsm/kg/year. Protein: This test detects the presence of overt proteinuria (>300 mg/day). However, normal urinary protein excretion is <30 mg/day. The presence of microalbuminuria (30-300 mg/day) is not detected by this method. Overt proteinuria is seen in both renal (eg, glomerulonephritis, renal tubular diseases, pyelonephritis) and nonrenal diseases (eg, myeloma, congestive heart failure, dehydration). Reference values for protein: <22 mg/dL Reference values have not been established for patients <18 years of age. Reference values have not been established for patients >83 years of age. Glucose: The test is specific for glucose. No other substance excreted in urine is known to give a positive result, including other reducing substances (eg, galactose, fructose, and lactose). This test may be used to determine whether the reducing substance found in urine is glucose. Glucosuria occurs when the renal threshold for glucose is exceeded (typically >180 mg/dL); this is most commonly, although not exclusively, seen in diabetes. Reference values for glucose: <or =15 mg/dL pH: Urine pH is affected by diet, medications, systemic acid-base disturbances, and renal tubular function. pH may affect urinary stone formation. For example, urine pH <6.0 may help reduce the tendency for calcium phosphate stones and pH >6.0 may reduce the tendency for uric acid stone formation. Ketones: Produced during metabolism of fat, increased ketones may occur during physiological stress conditions such as fasting, pregnancy, strenuous exercise, and frequent vomiting. In diabetics who are unable to efficiently utilize glucose due to a lack of insulin, starvation, or with other abnormalities of carbohydrate or lipid metabolism, ketones may appear in the urine in large amounts before serum ketone is elevated. Bilirubin: Bilirubinuria is an indicator of liver disease and biliary tract obstruction. Hemoglobin: Hemoglobinurinosis is an indicator of intravascular hemolysis. The test is equally sensitive to myoglobin as to hemoglobin. The presence of hemoglobin, in the absence of RBCs, is consistent with intravascular hemolysis. RBCs may be missed if lysis occurred prior to analysis; the absence of RBCs should be confirmed by examining a fresh specimen. The presence of myoglobin may be confirmed by MYGLU / Myoglobin. Reducing Substances: Urine can contain a variety of reducing substances (sugars [glucose, galactose, sucrose, fructose, lactose, maltose], ascorbic acid, drugs, etc), compounds so termed because of their ability to
reduce cupric ions. The primary reducing substances of medical significance are the sugars, glucose (diabetes), and galactose (galactosemia). Other sugars may be found but are not of clinical significance. Because glucose also is detected by glucose-specific dipstick reagents, the test for reducing substances is performed to detect galactose. Microscopy: RBCs, WBCs, renal tubular epithelial (RTE) cells, transitional epithelial cells, squamous epithelial cells, casts, sperm, free fat, oval fat bodies, bacteria, and pathologic crystals are reported. RBC casts are almost always indicative of glomerulonephritis. White cell casts are typically an indication of acute interstitial nephritis or pyelonephritis, but can also be seen in glomerulonephritides because there is often a component of accompanying interstitial nephritis. Fatty casts and free fat are often seen in patients with nephrotic syndrome or other glomerular diseases associated with significant proteinuria. Granular casts are observed in a number of disorders and are thought to be formed from partially degraded cellular casts, or are protein-derived casts. Hyaline casts are not thought to be indicative of any disease process, but increased numbers may be seen in concentrated urine specimens. Waxy casts and broad casts are most often observed in advanced renal failure. Increased numbers of RTE cells are indicators of renal tubular injury. Increased numbers of RTE may be caused by drugs with renal tubular toxicity (eg, cyclosporine A, aminoglycosides, cisplatin, radio-contrast media, acetaminophen overdose), interstitial nephritis, hypotension (surgical, sepsis, obstetric complications), or heme pigments from hemoglobinuria or myoglobinuria from rhabdomyolysis (eg, alcoholism, heat stroke, seizures, sickle cell trait). Newborns often shed RTE cells in their urine. The presence of squamous cells suggests that the specimen may not have been an optimal clean-catch specimen and could be contaminated with skin flora. Recommendations by an American Urological Association panel, based upon careful review of all available published outcome studies that contained results of detailed hematuria workups within actual patient populations, are that patients with more than 3 RBCs per high-power field in 2 out of 3 properly collected urine specimens should be considered to have microhematuria and, hence, evaluated for possible pathologic causes. However, the panel also noted that there is no absolute lower limit for hematuria, and risk factors for significant disease should be taken into consideration before deciding to defer an evaluation in patients with only 1 or 2 RBCs per high-power field. High-risk patients, especially those with a history of smoking or chemical exposure, should still be considered for a full urologic evaluation even after a properly performed urinalysis documented the presence of at least 3 RBCs per high-power field. In certain patients, even 1 or 2 RBCs per high-powered field might merit evaluation.(1)

Reference Values:
Descriptive report


Uroporphyrinogen Decarboxylase (UPG D), Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common porphyria resulting from a partial deficiency of hepatocyte and/or erythrocyte uroporphyrinogen decarboxylase (UROD). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in <5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All
forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. The work-up of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

**Useful For:** Diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria Due to limited stability for this test, the preferred test for analysis of UPGD enzyme is UPGD / Uroporphyrinogen Decarboxylase (UPG D), Whole Blood.

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
- >1.0 Relative Units (normal)
- 0.80-0.99 Relative Units (indeterminate)
- <0.80 Relative Units (porphyria cutanea tarda or hepatoerythropoietic porphyria)

**Clinical References:**

**Uroporphyrinogen Decarboxylase (UPG D), Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Porphyrria cutanea tarda (PCT) is the most common porphyria resulting from a partial deficiency of hepatocyte and/or erythrocyte uroporphyrinogen decarboxylase (UROD). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in <5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage.
Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

**Useful For:** This test is the preferred test for the confirmation of a diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
> 1.0 Relative Units (normal)
0.80-0.99 Relative Units (indeterminate)
< 0.80 Relative Units (porphyria cutanea tarda or hepatoerythropoietic porphyria)

**Clinical References:**

**Uroporphyrinogen III Synthase (Co-Synthase) (UPG III S), Erythrocytes**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Congenital erythropoietic porphyria (CEP) is an extremely rare, autosomal recessive porphyria that typically presents in early infancy. Also known as Gunther disease, CEP results from a deficiency of uroporphyrinogen III (co-) synthase (URO III S). In most cases, the disorder is suggested during the first few days or weeks of life by pink, violet, or brown urinary staining of diapers. Clinical symptoms include hemolytic anemia, hepatosplenomegaly, skin photosensitivity, scarring and blistering, red or brown dental discoloration (erythrodontia), and hypertrichosis (excess body hair). Growth and cognitive developmental delays are commonly observed in individuals with CEP. A few cases of adult-onset CEP have been reported, typically associated with a myelodysplastic syndrome. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Cutaneous) Testing Algorithm in Special Instructions or contact Mayo Medical Laboratories to discuss testing strategies.

**Useful For:** Diagnosis of congenital erythropoietic porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
> or =75 Relative Units (normal)

See The Heme Biosynthetic Pathway in Special Instructions.

**Clinical References:**

**FUROC**

**UroVysion for Detection of Bladder Cancer, Urine**

**Clinical Information:** Cystoscopy and urine cytology have been the primary methods for detecting urothelial carcinoma (UC). Unfortunately urine cytology has relatively poor sensitivity for the detection of recurrent UC. This is problematic because patients who have undetected recurrent tumors may have tumor progression that places them at increased risk of developing metastatic UC. The UroVysion assay is a FISH assay for the detection of recurrent UC. The UroVysion probe set contains probes to the centromeres of chromosomes 3, 7, and 17, and a locus-specific probe to the 9p21 band (site of the P16 tumor suppressor gene). The UroVysion assay detects cells with chromosomal abnormalities that are consistent with a diagnosis of UC. Studies have shown that the assay has higher sensitivity than urine cytology but similar specificity for the detection of recurrent UC. The UroVysion assay also demonstrates higher specificity than the BTA-stat assay for recurrent UC. See Fluorescence In Situ Hybridization for the Detection of Urothelial Carcinoma in Publications.

**Useful For:** Monitoring for tumor recurrence in patients with a history of urothelial carcinoma involving the bladder or upper urinary tract. Assessing patients with hematuria for urothelial carcinoma.

**Interpretation:** Lower Tract Samples Abnormal: any specimen satisfying 1 of the following criteria: -Four or more cells with gains of 2 or more chromosomes -Ten or more cells with a gain of a single chromosome or 10 or more cells with tetrasomic signal patterns (ie, 4 copies for each of the 4 probes) -Homozygous deletion of the 9p21 locus in > or =20% of the cells analyzed For cases that are abnormal, the percentage of abnormal cells and type of chromosomal abnormality (ie, polysomy, trisomy, tetrasomy, or homozygous 9p21 deletion) are indicated in the test report. Negative: -Fewer than 4 cells with gains of 2 or more chromosomes -Fewer than 10 cells with gain of a single chromosome or tetrasomy -Less than 20% of cells with homozygous 9p21 deletion

Upper Tract Samples Abnormal: any upper tract specimen satisfying 1 of the following criteria: -Four or more hypertetrasomy cells with at least 5 copies of 2 or more chromosomes -Ten or more cells with a gain of a single chromosome or > or =10% or more cells with tetrasomic or near-tetrasomic signal patterns (ie, 4 copies for each of the 4 probes) -Homozygous deletion of the 9p21 locus in > or =20% of the cells analyzed Negative: -Fewer than 4 cells with hypertetrasomy with at least 5 copies of 2 or more chromosomes -Fewer than 10% with tetrasomy -Less than 20% of cells with homozygous 9p21 deletion

**Reference Values:**
An interpretive report will be provided.


**USPF**

**USP6 (17p13), Aneurysmal Bone Cyst and Nodular Fasciitis, FISH, Tissue**

**Clinical Information:** Aneurysmal bone cyst (ABC) is a multicystic and expansile bone tumor of uncertain line of differentiation. USP6 rearrangements are detectable in approximately 70% of primary ABC and not in other conditions that may simulate ABC histologically, including giant cell tumor of bone, osteosarcoma, osteoblastoma, brown tumor, cherubism, and vascular neoplasms. Nodular fasciitis
(NF) is a self-limited mesenchymal lesion of myofibroblastic differentiation. NF’s rapid growth, rich cellularity, and brisk mitotic activity may lead to a misdiagnosis of sarcoma. USP6 rearrangements are detectable in 90% of NF but not in other conditions that may simulate NF, including dermatofibroma, cellular fibrous histiocytoma, fibromatosis, and a large variety of sarcomas.

**Useful For:** Supporting the diagnosis of aneurysmal bone cyst or nodular fasciitis

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the USP6 FISH probe (positive result). A positive result is consistent with rearrangement of the USP6 gene locus on 17p13 and supports the diagnosis of aneurysmal bone cyst (ABC) or nodular fasciitis (NF). A negative result is consistent with no rearrangement of the USP6 gene locus on 17p13. However, this result does not exclude the diagnosis of ABC or NF. Rearrangement varies in individual tumors and among different cells in the same tumor.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**
3. Fletcher CDM, Unni KK, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC Press, Lyon, France, 2005, pp 48-49

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**Ustilago nuda, Mold Grain Rust, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceeds as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

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**Uveal Melanoma, Chromosome 3 Monosomy, FISH, Tissue**

**Clinical Information:** Uveal melanoma is the most common type of primary intraocular malignancy in adults, with an annual incidence of 6 per million. These melanomas arise within pigmented cells of the uveal tract of the eye, which consists of the choroid, ciliary body, and iris. Overall, mortality rates in patients with uveal melanoma are quite high (approximately 50%) and are due to metastatic disease. Identifying patients likely to develop metastasis is critical for establishing patient prognosis. Previous studies have demonstrated that monosomy 3 is highly correlated with the development of metastatic disease in patients with uveal melanoma.

**Useful For:** As an aid to prognosis in patients with uveal melanoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for chromosome 3 probe set. A positive result is consistent with monosomy 3 and a higher risk for metastatic disease in uveal melanoma patients. A negative result suggests that aneuploidy of chromosome 3 is not present.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Valproic Acid, Free and Total, Serum**

**Clinical Information:** Valproic acid (valproate, Depakote, or Depakene) is an effective medication for absence seizures, generalized tonic-clonic seizures, and partial seizures, when administered alone or in conjunction with other antiepileptic agents. The valproic acid that circulates in blood is 85% to 90% protein-bound under normal circumstances. In uremia or during concomitant therapy with other drugs that are highly protein-bound (such as phenytoin), valproic acid is displaced from protein, resulting in a higher free fraction of the drug circulating in blood. Since neurologic activity and toxicity of valproic acid are directly related to the unbound fraction of drug, adjustment of dosage based on knowledge of the free valproic acid concentration may be useful in the following situations: concomitant use of highly protein-bound drugs (usually >80% bound), hypoalbuminemia, pregnancy, renal or hepatic failure, and in...
the elderly. In these situations, the total valproic acid concentration in the blood may underestimate the disproportionately higher free valproic acid fraction.

**Useful For:** Monitoring both total and free valproic acid levels in therapy Assessing compliance Evaluating potential toxicity

**Interpretation:** The generally acceptable range for total valproic acid used as a reference to guide its therapy is 50 to 125 mcg/mL. The corresponding range of free valproic acid concentration for clinical reference is 5 to 25 mcg/mL. Low free valproic acid concentration relative to these ranges may suggest inadequate dosing, while a high free valproic acid concentration may be associated with toxic effects. Because the concentration of valproic acid fluctuates considerably depending on the time from last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

**Reference Values:**

**VALPROIC ACID, TOTAL**
- Therapeutic: 50 (trough)-125 (peak) mcg/mL
- Critical value: > or =151 mcg/mL

**VALPROIC ACID, FREE**
- Therapeutic: 5-25 mcg/mL
- Critical value: >30 mcg/mL

Valproic Acid, Total, Serum

**Clinical Information:** Valproic acid (valproate, Depakote, or Depakene) is used for treatment of simple and complex absence seizures and as combination therapy with other anticonvulsants for control of generalized seizures that include absence seizures. Valproic acid is initially dosed at 15 mg/kg/day, with dosage increases over time to a maximum of 60 mg/kg/day. The volume of distribution of valproic acid is 0.2 L/kg and its half-life is 10 to 14 hours in adults, and shorter in children. It is approximately 90% protein bound. Hepatic failure and a Reyes-like syndrome associated with administration of valproic acid at therapeutic levels have been reported. Careful monitoring of liver function during the first 6 months of therapy is required. Major side effects such as central nervous system depression, thrombocytopenia, and hepatic dysfunction are likely to be experienced if the peak level regularly is >125 mcg/mL. Analysis of free valproic acid levels may be useful in delineating the cause of toxicity when the total concentration is not excessive. Valproic acid exhibits substantial effects on the pharmacology of phenytoin, whereas phenytoin exhibits only a limited effect on valproic acid. This is due to the relative abundance of the 2 drugs in the body. Valproic acid is present at a 2- to 3-fold mass excess and a 5- to 7-fold molar excess.

**Useful For:** Monitoring total valproic acid in therapy Assessing compliance Evaluating potential toxicity

**Interpretation:** Optimal response is usually observed when the trough level is >50 mcg/mL. Peak levels should not exceed 125 mcg/mL.

**Reference Values:**
- Therapeutic: 50 (trough)-125 (peak) mcg/mL
- Critical value: > or =151 mcg/mL

**Clinical References:**

Vanadium, Serum

**Clinical Information:** The element vanadium, naturally found in minerals and rocks, is considered an essential element for mammals, although conclusive evidence for humans is lacking. Animal studies have shown that vanadium is essential for mammalian growth and reproduction, iron and lipid metabolism, and RBC production. Vanadium is recovered from minerals or as a by-product of iron, titanium, and uranium refining. Vanadium pentoxide is used in the production of special steels. Vanadium compounds are used as catalysts for polypropylene production and synthesis of inorganic and organic chemicals. Vanadium compounds are used in dyes, photography, ceramics, and in the production of special glasses. Vanadium also is a component of a fiber mesh prosthetic alloy. The main source of vanadium intake for the general population is food, with an estimated daily intake of 20 mcg, of which most is excreted in the feces, without absorption. Absorption through the inhalation route results in more effective uptake. About 90%
of blood vanadium is found in serum. The half-life in serum is not well documented, but it appears to be on the order of several days. Although there is minimal evidence for the nature of vanadium complexation in the body, research suggests transferrin will bind available ionized vanadium. Currently, there is no clinical data to support the need for taking vanadium supplements such as vanadyl sulfate, vanadium colloid, or any other form. This test provides no information regarding any theoretical vanadium deficiency. Vanadium has been recognized as an occupational hazard for >20 years. Elevated atmospheric vanadium levels can result from burning fossil fuels with a high vanadium content. Inhalation and ingestion are the primary exposure routes. Vanadium exposure can result in a metallic taste and so-called "green tongue." Sensitization can result in asthma or eczema. Vanadium intoxication is effectively treated with ascorbic acid. Increased vanadium serum concentrations are observed in dialysis patients and those with compromised renal function since the kidney is primarily responsible for vanadium elimination. Elevated serum vanadium levels have been observed in patients with joint replacements; concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting vanadium toxicity Monitoring metallic prosthetic implant wear

Interpretation: Values <1.0 ng/mL are normal. Values >5.0 ng/mL indicate probable exposure. Prosthesis wear is known to result in increased circulating concentration of metal ions.(2-3) Modest increase (1-2 ng/mL) in serum vanadium concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations >5 ng/mL in a patient with a vanadium-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
Normal: <1.0 ng/mL


VANPA 37069

Vancomycin, Peak, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Staphylococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/amoxicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta lactams. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients comatted with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain >10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

Useful For: Monitoring peak levels in selected patients receiving vancomycin therapy

Interpretation: Typical peak levels are between 25.0 and 50.0 mcg/mL.

Current as of July 8, 2016 11:28 am CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
VANRA 37071

Vancomycin, Random, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Staphylococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta lactams. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain >10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic studies or for select patients.

Useful For: Monitoring adequacy of drug concentration during vancomycin therapy. This test is used whenever a specimen is submitted or collected without collection timing information. Random levels may be ordered when attempting to determine when to dose vancomycin in patients with renal impairment or those undergoing dialysis.

Interpretation: Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 and 20.0 mcg/mL, depending on the type of infection. Peak levels are not recommended for monitoring, except in select circumstances such as when performing pharmacokinetic analyses (eg, area under the curve: AUC determinations). Typical peak levels are between 25.0 and 50.0 mcg/mL.

Reference Values:
Vancomycin, Trough
Therapeutic: 10.0-20.0 mcg/mL

Vancomycin, Peak
Therapeutic: 25.0-50.0 mcg/mL


VANTA 37070

Vancomycin, Trough, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Staphylococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta lactams. Vancomycin has been associated with...
nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain >10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

**Useful For:** Trough concentrations drawn at steady-state are the preferred test for monitoring vancomycin therapy

**Interpretation:** Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 to 20.0 mcg/mL, depending on the type of infection.

**Reference Values:**
Therapeutic: 10.0-20.0 mcg/mL

**Clinical References:**

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**VRERP 84406**

**Vancomycin-Resistant Enterococcus, Molecular Detection, PCR**

**Clinical Information:** Vancomycin-resistant enterococci (VRE) are major nosocomial pathogens. Patients who are particularly vulnerable to fatal disease from VRE include those with hematologic malignancies and liver transplants. Nosocomial spread of VRE occurs as the result of fecal carriage. Risks for both colonization and infection include prolonged hospitalization, intensive care unit stay, transplantation, hematologic malignancies, and prolonged exposure to antibiotics. The Centers for Disease Control and Prevention provides recommendations to prevent the spread of VRE in institutional settings. These recommendations include isolation of patients experiencing active VRE infection, screening of patients by perianal swab or fecal testing to identify carriers of VRE, and subsequent isolation or cohorting of VRE carriers. Identification and isolation of VRE carriers has been shown to be cost-effective. In Enterococcus faecalis or Enterococcus faecium, vancomycin resistance is usually associated with the presence of the vanA or vanB genes. The presence of these genes is detected by a molecular method in this assay.

**Useful For:** Identifying carriers of vancomycin-resistant enterococci

**Interpretation:** Positive test results indicate the presence of either the vanA or vanB gene, which confers vancomycin resistance in Enterococcus faecalis and Enterococcus faecium (and occasionally other organisms). Patients with a positive test result should be placed in isolation or cohorted with other vancomycin-resistant enterococci (VRE) carriers according to the institution's infection control practices. A negative result indicates the absence of detectable vanA or vanB DNA in the specimen but does not rule out carrier status as false-negative results may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of VRE in quantities less than the limit of detection of the assay. In the rare event that PCR testing appears to be negative but there is evidence of PCR inhibition, the result will read "PCR inhibition present," in such a case, a new specimen should be submitted for repeat testing.

**Reference Values:**
Not applicable

**Clinical References:**
2. Mayo Medical Laboratories Communique: Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLabs.com Page 207

**FVANG**

### Vanilla IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**VANIL**

### Vanilla, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
</tbody>
</table>

Vanillylmandelic Acid (VMA) and Homovanillic Acid (HVA), Random, Urine

Clinical Information: Elevated values of homovanillic acid (HVA), vanillylmandelic acid (VMA), and other catecholamine metabolites (eg, dopamine) may be suggestive of the presence of a catecholamine-secreting tumor (eg, neuroblastoma, pheochromocytoma, or other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism: monamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

Useful For: First preferred test for screening for catecholamine-secreting tumors in a random urine specimen when requesting both homovanillic acid and vanillylmandelic acid Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

Interpretation: Homovanillic acid (HVA) and vanillylmandelic acid (VMA) concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA and VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

Reference Values:

VMA

- <1 year: <25.0 mg/g creatinine
- 1 year: <22.5 mg/g creatinine
- 2-4 years: <16.0 mg/g creatinine
- 5-9 years: <12.0 mg/g creatinine
- 10-14 years: <8.0 mg/g creatinine
- > or =15 years: <7.0 mg/g creatinine

HVA

- <1 year: <35.0 mg/g creatinine
- 1 year: <30.0 mg/g creatinine
- 2-4 years: <25.0 mg/g creatinine
- 5-9 years: <15.0 mg/g creatinine
- 10-14 years: <9.0 mg/g creatinine
- > or =15 years: <8.0 mg/g creatinine

**Vanillylmandelic Acid (VMA), 24 Hour, Urine**

**Clinical Information:** Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid [HVA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of 1 of the above-mentioned tumors.

**Useful For:** Screening children for catecholamine-secreting tumors with a 24 hour urine collection when requesting vanillylmandelic acid only Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

**Interpretation:** Vanillylmandelic acid and/or homovanillic acid concentrations are elevated in most patients (more than 90%) with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated values are suggestive of a pheochromocytoma, but they are not diagnostic.

**Reference Values:**
- <1 year: <25.0 mg/g creatinine
- 1 year: <22.5 mg/g creatinine
- 2-4 years: <16.0 mg/g creatinine
- 5-9 years: <12.0 mg/g creatinine
- 10-14 years: <8.0 mg/g creatinine
- ≥15 years (adults): <8.0 mg/24 hours

**Clinical References:**

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**Vanillylmandelic Acid (VMA), Random, Urine**

**Clinical Information:** Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid [HVA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of 1 of the above-mentioned tumors.

**Useful For:** Screening children for catecholamine-secreting tumors with a random urine collection when requesting vanillylmandelic acid only Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

**Interpretation:** Vanillylmandelic acid (VMA) and/or homovanillic acid concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

**Reference Values:**
- <1 year: <25.0 mg/g creatinine
- 1 year: <22.5 mg/g creatinine

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FVZD 91752 Varicella Zoster Antigen, DFA
Reference Values:
Not Detected

VZPG 34944 Varicella-Zoster Antibody, IgG, Serum
Clinical Information: Varicella-zoster virus (VZV), a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and herpes zoster (shingles). Chickenpox is a highly contagious, though typically benign disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV will aid in identifying nonimmune individuals.

Useful For: Determination of immune status of individuals to the varicella-zoster virus (VZV)
Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

Interpretation: Positive: Antibody index value (AI) ≥ 1.1 The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cut-off for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies indicates prior exposure to the varicella-zoster virus (VZV) through infection or immunization. Individuals testing positive are considered immune to varicella-zoster. Equivocal: AI 0.9-1.0 Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI < 0.8 The absence of detectable IgG-class antibodies suggests no prior exposure to the VZV or the lack of a specific immune response to immunization.

Reference Values:
Vaccinated: Positive (> or ≥ 1.1 AI)
Unvaccinated: Negative (< or < 0.8 AI)

Varicella-Zoster Antibody, IgM and IgG (Separate Determinations), Serum

Clinical Information: Varicella-zoster virus (VZV), a herpesvirus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious, though typically benign disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV will aid in identifying nonimmune individuals. The presence of IgM-class antibodies to VZV is suggestive of acute or recent infection; however, results should be correlated with clinical presentation.

Useful For: Laboratory diagnosis of acute/recent infection with varicella-zoster virus (VZV) Determination of immune status of individuals to the VZV Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

Interpretation: A positive IgG result coupled with a positive IgM result suggests recent infection with varicella-zoster virus (VZV). This result should not be used alone to diagnose VZV infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with VZV. These individuals are considered to have protective immunity to reinfection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to VZV and nonimmunity. However, a negative result does not rule out a VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infections should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

Reference Values:
IgM
Negative (reported as negative or positive)

IgG
Vaccinated: positive (> or =1.1 AI)
Unvaccinated: negative (< or =0.8 AI)

Clinical Information: Varicella-zoster virus (VZV), a herpes virus, causes 2 exanthematous (rash-associated) diseases, chickenpox and herpes zoster (shingles). Chickenpox is a highly contagious disease usually contracted during childhood and is characterized by a dermal vesiculopustular rash that develops in successive crops. Although primary infection results in immunity to subsequent exposure to chickenpox, the virus remains latent in the body, localized to the dorsal root or cranial nerve ganglia. Reactivation of latent infection manifests as herpes zoster. On reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash usually limited to a single dermatome. Reactivation occurs in older adults and in patients with impaired cellular immunity. Several populations are at risk of suffering unusually severe reactions to VZV infections. The infection in pregnant women may spread through the placenta to the fetus, causing congenital disease in the infant. Immunocompromised patients in hospitals may contract severe nosocomial infections from others who have active VZV infections. Therefore, serologic screening of direct health care providers (physicians, allied health care personnel) and individuals in high-risk groups is necessary to avoid uncontrolled spread of infection. While the clinical presentation of VZV infection is generally characteristic, serologic evaluation of patients with atypical and systemic infections is often required. For example, it is extremely important to serologically evaluate patients for the early detection of VZV infections in hospital settings. Nosocomial spread of VZV infection can be life-threatening to immunocompromised patients susceptible to infection.

Useful For: Diagnosing acute-phase infection with varicella-zoster virus

Interpretation: A positive IgM result indicates a recent infection with varicella-zoster virus (VZV). A negative result does not rule out the diagnosis of VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infection should be followed by testing a new specimen in 2 to 3 weeks.

Reference Values:
Negative (reported as positive or negative)


FVZGC

Varicella-Zoster Virus Antibody, IgG, CSF

Interpretation: The detection of antibodies to varicella-zoster in CSF may indicate central nervous system infection. However, consideration must be given to possible contamination by blood or transfer of serum antibodies across the blood-brain barrier.

Reference Values:
134 IV or less: Negative â€“ No significant level of IgG antibody to varicella-zoster virus detected.
135 â€“ 165 IV: Equivocal â€“ Repeat testing in 10 â€“ 14 days may be helpful.
166 IV or greater: Positive â€“ IgG antibody to varicella-zoster virus detected, which may indicate a current or past varicella-zoster infection.

LVZV

Varicella-Zoster Virus, Molecular Detection, PCR

Clinical Information: Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before 10 years of age. After primary infection with VZV, the virus persists in latent form and may emerge (usually in adults 50 years of age and older) clinically to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).
**Useful For:** Rapid (qualitative) detection of varicella-zoster virus DNA in clinical specimens for laboratory diagnosis of disease due to this virus

**Interpretation:** Detection of varicella-zoster virus (VZV) DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler PCR assay does not yield positive results with other herpesvirus gene targets (herpes simplex virus, cytomegalovirus, Epstein-Barr virus).

**Reference Values:**

**Negative**

**Clinical References:**

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**FVEGF**

**Vascular Endothelial Growth Factor (VEGF), ELISA**

**Reference Values:**

31–86 pg/mL

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**VIP**

**Vasoactive Intestinal Polypeptide (VIP), Plasma**

**Clinical Information:** Vasoactive intestinal polypeptide (VIP) was originally isolated from porcine small intestine and was recognized by its potent vasodilator activity. This brain/gut hormone has widespread distribution and is present in neuronal cell bodies localized in the central nervous system, digestive, respiratory, and urogenital tracts, exocrine glands, and thyroid and adrenal glands. VIP has a wide scope of biological actions. The main effects of VIP include relaxation of smooth muscle (bronchial and vascular dilation), stimulation of gastrointestinal water and electrolyte secretion, and release of pancreatic hormones. VIP-producing tumors (VIPomas) are rare; most (90%) are located in the pancreas. Watery diarrhea, hypokalemia, and achlorhydria are key symptoms.

**Useful For:** Detection of vasoactive intestinal polypeptide producing tumors in patients with chronic diarrheal diseases

**Interpretation:** Values >75 pg/mL may indicate the presence of an enteropancreatic tumor causing hypersecretion of vasoactive intestinal polypeptide (VIP). Values >200 pg/mL are strongly suggestive of VIP-producing tumors (VIPoma). VIPoma is unlikely with a 24-hour stool volume <700 mL.

**Reference Values:**

<75 pg/mL

**Clinical References:**
**VDRL, Spinal Fluid**

**Clinical Information:** The Venereal Disease Research Laboratory (VDRL) is a nontreponemal serologic test for syphilis that uses a cardiolipin-cholesterol-lecithin antigen to detect reaginic antibodies. The presence of neurosyphilis in untreated patients can be detected by the presence of pleocytosis, elevated protein, and a positive VDRL.

**Useful For:** Aiding in the diagnosis of neurosyphilis

**Interpretation:** A positive Venereal Disease Research Laboratories (VDRL) on spinal fluid is highly specific for neurosyphilis. Positive results will be titrated.

**Reference Values:**
- Negative
- Positive results will be titrated.

**Clinical References:** Miller JN: Value and limitations of nontreponemal and treponemal tests in the laboratory diagnosis of syphilis. Clin Obstet Gynecol 1975;18:191-203

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**Vegetables Panel IgG**

**Reference Values:**
- Alfalfa (Medicago sativa) IgG

<table>
<thead>
<tr>
<th>IgG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagus</td>
<td>Antibody levels greater than the reference range indicate that the patient has been immunologically sensitized to the antigen. The significance of elevated IgG depends on the nature of the antigen and the patient's clinical history. The test method was the Phadia ImmunoCAP.</td>
</tr>
<tr>
<td>Avocado</td>
<td></td>
</tr>
<tr>
<td>Beet Root</td>
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<td>Broccoli</td>
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<tr>
<td>Cabbage</td>
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<tr>
<td>Carrot</td>
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</tr>
<tr>
<td>Celery</td>
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</tr>
<tr>
<td>Cucumber</td>
<td></td>
</tr>
<tr>
<td>Garlic</td>
<td></td>
</tr>
<tr>
<td>Pepper Bell/Paprika (C.annuum)</td>
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</tr>
<tr>
<td>Lettuce</td>
<td></td>
</tr>
<tr>
<td>Mushroom</td>
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</tr>
<tr>
<td>Olive Black</td>
<td></td>
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<td>Onion</td>
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<tr>
<td>Pea Green</td>
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<td>Potato Sweet</td>
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<tr>
<td>Potato White</td>
<td></td>
</tr>
<tr>
<td>Spinach</td>
<td></td>
</tr>
<tr>
<td>Bean Green/String</td>
<td></td>
</tr>
</tbody>
</table>
Tomato IgG

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situation to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**VELV**

82917

**Velvet Leaf, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Venlafaxine, Serum**

**Clinical Information:** Venlafaxine is a serotonin and norepinephrine reuptake inhibitor approved for treatment of major depression, anxiety and panic disorders, and social phobias. It is also used for bipolar disorder, bulimia, post-traumatic stress, obsessive behavior, and attention-deficit disorder. Venlafaxine is converted by CYP2D6 to the active metabolite, O-desmethylvenlafaxine. The therapeutic range for venlafaxine includes measurement if O-desmethylvenlafaxine; optimal response is seen when combined concentrations of parent and metabolite are between 195 and 400 ng/mL. Venlafaxine is significantly affected by reduced hepatic function, but only slightly by reduced renal function. Average elimination half-lives are 5 hours for venlafaxine and 10 hours for O-desmethylvenlafaxine, which are much shorter than many other antidepressants. For this reason, extended release formulations are available. Time to peak serum concentration is 2 hours for the regular product and 8 hours for the extended release product. Common toxicities are mild, including drowsiness, dizziness, nausea, and headache.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be used to evaluate patient compliance.

**Interpretation:** Most individuals display optimal response to venlafaxine when combined serum levels of venlafaxine and O-desmethylvenlafaxine are between 195 and 400 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels >1,000 ng/mL. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

Venlafaxine + O-desmethylvenlafaxine: 195-400 ng/mL

**Clinical References:**


**Venom Bumble Bee (Bombus terrestris) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 50.0-99.99 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

**Venom Honey Bee IgG**

**Reference Values:**

>3.5 mcg/mL

Venom IgG Reference Values: 1.0 â€“ 3.5 mcg/mL Low venom IgG indicating a significant reaction risk. 3.5 â€“ 6.0 mcg/mL Moderate level of venom IgG that may be associated from serious sting reactions (J.Clin.Immun.6:172, 1983) > 6.0 mcg/mL Elevated venom IgG usually associated with protection from serious sting reactions (J.Clin.Immun.6:172, 1983) The interpretative guidelines have been adapted from Golden et al (JACI 1992; 90:386-393). The test method used is the Phadia ImmunoCAP IgG assay which has been recalibrated to correlate with the venom IgG assay referenced above.

**Venom W-F Hornet IgG**

**Reference Values:**

>3.5 mcg/mL
**Reference Values:**

>3.5 mcg/mL

Venom IgG Reference Values: 1.0 ≤ 3.5 mcg/mL Low venom IgG indicating a significant reaction risk. 3.5 ≤ 6.0 mcg/mL Moderate level of venom IgG that may be associated with serious sting reactions (J.Clin.Immun.6:172, 1983) > 6.0 mcg/mL Elevated venom IgG usually associated with protection from serious sting reactions (J.Clin.Immun.6:172, 1983) The interpretative guidelines have been adapted from Golden et al (JACI 1992; 90:386-393). The test method used is the Phadia ImmunoCAP IgG assay which has been recalibrated to correlate with the venom IgG assay referenced above.

**VLCZ**

**Very Long Chain Acyl-CoA Dehydrogenase Deficiency, Full Gene Analysis**

**Clinical Information:** Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is an autosomal recessive disorder of mitochondrial fatty acid beta-oxidation. Mitochondrial beta-oxidation plays a major role in energy production and VLCAD catalyzes the first step in the breakdown of fatty acids that are 14 to 20 carbons long. VLCAD deficiency has a reported incidence of approximately 1 in 30,000 births and has a variable age of onset that is generally classified into 3 categories. Individuals with the early-onset type present with cardiomyopathy, hypotonia, and hepatomegaly in the first months of life; sudden death is also frequent. Individuals with the early-childhood onset type typically present with hypoketotic hypoglycemia and hepatomegaly without cardiomyopathy. Individuals with the late-onset type of VLCAD deficiency generally present after childhood with intermittent rhabdomyolysis and muscle dysfunction that often manifests as muscle cramps and exercise intolerance. Review of clinical features and biochemical analysis via plasma acylcarnitines, plasma fatty acid profile, urine organic acids, and fibroblast fatty acid oxidation probe studies are recommended as laboratory evaluations for VLCAD deficiency. Plasma and urine biochemical testing are not reliable for identifying all individuals with VLCAD deficiency or confirming carrier status, as biochemical findings may normalize during periods of good metabolic control. It is uncertain whether skin fibroblast analysis can identify carriers of VLCAD deficiency. The diagnosis is confirmed by molecular testing. Mutations in the ACADVL gene are responsible for VLCAD deficiency. Most mutations are family specific with the exception of the V283A mutation (also reported in the literature as V243A). This mutation is estimated to account for 20% of pathogenic alleles in patients identified by newborn screening. When this test is ordered, results of biochemical assays should be included with the specimen as they are necessary for accurate interpretation of the VLCAD sequence analysis.

**Useful For:** Confirmation of a diagnosis of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency Carrier screening in cases where there is a family history of VLCAD deficiency, but an affected individual is not available for testing or disease-causing mutations have not been identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


**VHLE**

**VHL Gene, Erythrocytosis Mutation Analysis**

Current as of July 8, 2016 11:28 am CDT

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Page 2018
**Clinical Information:** Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera, or secondary, in response to increased serum erythropoietin levels). Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and paraganglioma formation. It is caused by mutations in several genes, including VHL, and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and VHL can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL typically have normal p50 results. The true prevalence of hereditary erythrocytosis causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate-mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of HIF proline residues. Mutations resulting in altered VHL proteins can lead to familial erythrocytosis, type 2 (ECYT2; OMIM 263400). ECYT2 is a clinically heterogeneous disorder characterized by congenital erythrocytosis with or without high serum EPO levels, venous and arterial thrombosis, and pulmonary hypertension that can manifest as early as infancy but more typically into adulthood. An increased risk for tumors associated with von Hippel-Lindau syndrome, which is also caused by mutations in the VHL gene, has not been observed.

**Useful For:** Diagnosis of suspected JAK2-negative VHL-related erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

An interpretive report will be provided.


Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 2019
VHL Gene, Full Gene Analysis

Clinical Information: von Hippel-Lindau (VHL) disease is an autosomal dominant cancer predisposition syndrome with a prevalence of approximately 1 in 36,000 livebirths. It predisposes affected individuals to the development of mainly 5 different types of neoplasms: retinal angioma (approximately 5%-70% penetrance), cerebellar hemangioblastoma (CHB) (44%-72% penetrance), clear-cell renal cell carcinoma (cRCC) (approximately 25%-60% penetrance), spinal hemangioblastoma (SHB) (approximately 13%-50% penetrance), and pheochromocytoma (PC) (approximately 10%-20% penetrance). Angiomas in other organs, pancreatic cysts/adenomas/carcinomas, islet cell tumors, and endolymphatic sac tumors can also occur. VHL-related tumors typically present in the second to third decade of life, but sometimes earlier, particularly for retinal angiomas. For each tumor type, the incidence rates rise steadily, albeit at different slopes, throughout life. VHL disease is caused by heterozygous germline loss-of-function sequence variants, small deletions or insertions (approximately 80% of cases), or large germline deletions (approximately 20% of cases) of the VHL gene. Approximately 20% of cases are due to new (de novo) pathogenic variants, which in some cases result in disease mosaicism. This presents a diagnostic challenge for individuals who present with clinical signs of VHL disease, but test negative genetically because the pathogenic variant is not present in all peripheral leukocytes. VHL encodes the VHL protein, a tumor suppressor protein that is involved in ubiquitination and degradation of a variety of other proteins, most notably hypoxia-inducible factor (HIF). HIF induces expression of genes that promote cell survival and angiogenesis under conditions of hypoxia. It is believed that diminished HIF degradation due to inactive VHL protein causes the tumors in VHL disease. Tumors form when the remaining intact copy of VHL is somatically inactivated in target tissues (2-hit model). Sporadic cRCC, unrelated to VHL disease, also shows somatic deletions, sequence variants, or aberrant methylation in 80% to 100% of cases. Retinal angioma, CHB, and SHB cause morbidity and some mortality through pressure on adjacent structures and through retinal or subarachnoid hemorrhages. VHL-related cRCC and PC follow a similar clinical course as their sporadic counterparts, with substantial morbidity and mortality. Early detection of VHL-related tumors can reduce these adverse outcomes, and surveillance of affected individuals is, therefore, widely advocated. Genetic testing is the most accurate way to identify presymptomatic individuals, who can then be entered into a surveillance program. Research has suggested that certain combinations of VHL tumors cluster in VHL families, and this may be driven by the type of VHL gene variant present in the family. This observation has led to a phenotype-based classification of VHL syndrome. However, it should be noted that these patterns are not clear cut, and should not necessarily be used for diagnostic or therapeutic purposes. VHL Type 1: Retinal angioma, central nervous system (CNS) hemangioblastoma, renal cell carcinoma, pancreatic cysts, and neuroendocrine tumors. Low risk for pheochromocytoma. Associated with pathogenic truncating or missense variants that are predicted to grossly disrupt the folding of VHL protein. VHL Type 2: Pheochromocytoma, retinal angiomas, and CNS hemangioblastomas. High risk for pheochromocytoma. Associated with pathogenic missense variants. VHL Type 2 is further subdivided: -Type 2A: Pheochromocytoma, retinal angiomas, and CNS hemangioblastomas; low risk for renal cell carcinoma -Type 2B: Pheochromocytoma, retinal angiomas, CNS hemangioblastomas, pancreatic cysts, and neuroendocrine tumor; high risk for renal cell carcinoma -Type 2C: Risk for pheochromocytoma only Additionally, pathogenic sequence variants distinct from those associated with VHL syndrome can cause hereditary erythrocytosis or polycythemia. Cases of VHL disease and erythrocytosis are largely mutually exclusive, and patients who present with erythrocytosis do not typically develop the neoplasms discussed above, although they are sometimes associated with varicose veins and vertebral hemangiomas. Erythrocytosis due to VHL is caused by germline homozygous or compound heterozygous pathogenic sequence variants, and is inherited in an autosomal recessive manner. These patients usually have a markedly high erythropoietin level in the
presence of an elevated hematocrit. Erythrocytosis due to a germline homozygous missense variant at nucleotide c.598C->T, p.R200W in the VHL gene has been found endemically in the Chuvash region of Russia, leading individuals with this variant to be labeled as having Chuvash polycythemia (CP), although further studies have determined that this variant can be found in other ethnic groups as well. These patients are at an increased risk to develop cerebrovascular and embolic complications. Heterozygous carriers are typically unaffected.

**Useful For:** Diagnosis of suspected von Hippel-Lindau (VHL) disease Diagnosis of suspected VHL-related hereditary erythrocytosis

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.


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**Vibrio Culture, Stool**

**Clinical Information:** Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals) and these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician determine the appropriate testing to be performed. Vibrio cholerae, the causative agent of endemic, epidemic, and pandemic cholera, results in large volumes of rice-water stools due to the production of an enterotoxin. Severe dehydration is of concern in patients without access to adequate medical care. In the United States, Vibrio parahemolyticus is the most common cause of Vibrio disease. Vibrio parahemolyticus is associated with the consumption of raw shellfish or fish and results in gastroenteritis with nausea, vomiting, abdominal cramps, low-grade fever, and chills. Usually rehydration is the only treatment required, although in some cases, antimicrobial therapy is needed.

**Useful For:** Determining whether Vibrio species is the cause of diarrhea and, in turn, identifying the source of the infectious agent
**Interpretation:** The growth of Vibrio species identifies the cause of diarrhea.

**Reference Values:**
No growth


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**VIGA**

**Vigabatrin (Sabril)**

**Reference Values:**
Units: ug/mL

Therapeutic and toxic ranges have not been established.

Expected serum vigabatrin concentrations in patients receiving recommended daily dosages: 20 â€“ 160 ug/mL

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**FWVE**

**Vinegar Wine IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 - 49.99 Strong Positive 5 50.00 - 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**VIRNR**

**Viral Culture, Non-Respiratory**

**Clinical Information:** Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus, enteroviruses, herpes simplex virus, and varicella-zoster virus. Many viral infections (eg, herpes simplex virus, cytomegalovirus, varicella-zoster virus) can now be treated with antiviral drugs. Early laboratory diagnosis by isolation is very helpful in the medical management of these patients.

**Useful For:** Diagnosing viral infections

**Interpretation:** A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of this finding. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by this culture test include Epstein-Barr virus, rubella virus, papilloma, and Norwalk virus), and nonviable organisms submitted. For patients with diarrhea, see Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for other diagnostic tests that may be useful.

**Reference Values:**
Negative
If positive, virus is identified.

**Viral Culture, Respiratory**

**Clinical Information:** Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus, enteroviruses, herpes simplex virus, influenza virus, parainfluenza virus (types 1-3), respiratory syncytial virus, and varicella-zoster virus. Many viral infections can now be treated with antiviral drugs. Early laboratory diagnosis by isolation is very helpful in the medical management of these patients.

**Useful For:** Diagnosing viral infections

**Interpretation:** A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of this finding. Influenza virus infection is a state-mandated reportable disease. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by culture include Epstein-Barr virus, rubella virus, and papilloma virus), and nonviable organisms submitted. Parainfluenza virus type 4 may also not be detected by viral culture.

**Reference Values:**
- Negative
- If positive, virus is identified.

**Clinical References:**

**Viscosity, Serum**

**Clinical Information:** Viscosity is the property of fluids to resist flow. Hyperviscosity may be manifested by oronasal bleeding, blurred vision, headaches, dizziness, nystagmus, deafness, diplopia, ataxia, paresthesias, or congestive heart failure. Funduscopic examination reveals dilation of retinal veins and flame shaped retinal hemorrhages. The most common cause of serum hyperviscosity is the presence of large concentrations of IgM monoclonal proteins, and Waldenstrom's macroglobulinemia accounts for 80% to 90% of hyperviscosity cases. Hyperviscosity syndrome can also occur in multiple myeloma patients. Because the ability of a monoclonal protein to cause hyperviscosity is affected by its concentration, molecular weight, and aggregation, sera with concentrations of monoclonal IgM >4 g/dL, IgA >5 g/dL, or IgG >6 g/dL should be tested for hyperviscosity. Serum viscosity and electrophoresis are recommended before and after plasmapheresis in order to correlate viscosity and M-spike with patient symptoms. This correlation may be useful for anticipating the need for repeat plasmapheresis.

**Useful For:** Detection of increased viscosity Monitoring patients with hyperviscosity syndrome

**Interpretation:** Although viscosities >1.5 centipoises (cP) are abnormal, hyperviscosity is rarely present unless the viscosity is >3 cP.

**Reference Values:**
- > or =16 years: < or =1.5 centipoises
  - Reference values have not been established for patients that are <16 years of age.

**Clinical References:**
**Vitamin A and Vitamin E, Serum**

**Clinical Information:** Vitamin A: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene ingested and absorbed by the intestine (carotene is converted to vitamin A by intestine absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, with an increased incidence of death related to infectious diseases. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest >15 mg per day, and in children who ingest >6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension and bone demineralization may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg. Vitamin E: Vitamin E contributes to the normal maintenance of biomembranes, the vascular system, and the nervous systems; and provides antioxidant protection for vitamin A. The level of vitamin E in the blood plasma or serum after a 12- to 14-hour fast reflects the individual's reserve status. Currently, the understanding of the specific actions of vitamin E is very incomplete. The tocopherols (vitamin E and related fat-soluble compounds) function as antioxidants and free-radical scavengers, protecting the integrity of unsaturated lipids in the biomembranes of all cells and preserving retinol from oxidative destruction. Vitamin E is known to promote the formation of prostacyclin in endothelial cells and to inhibit the formation of thromboxanes in thrombocytes, thereby minimizing the aggregation of thrombocytes at the surface of the endothelium. Those influences on thrombocyte aggregation may be of significance in relation to risks for coronary atherosclerosis and thrombosis. Deficiency of vitamin E in children leads to reversible motor and sensory neuropathies; this problem also has been suspected in adults. Premature infants who require an oxygen-enriched atmosphere are at increased risk for bronchopulmonary dysplasia and retrolental fibroplasia. Supplementation with vitamin E has been shown to lessen the severity of, and may even prevent, those problems. In addition, low blood levels of vitamin E may be associated with abetalipoproteinemia, presumably as a result of a lack of the ability to form very low-density lipoproteins and chylomicrons in the intestinal absorptive cells of affected persons. Vitamin E toxicity has not been established clearly. Chronically excessive ingestion has been suspected as a cause of thrombophlebitis, although this has not been definitively verified. Deficiencies of vitamins A and E may arise from poor nutrition or from intestinal malabsorption. Persons, especially children, at risk include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia. Infantile cholangiopathies that may lead to malabsorption of vitamins A and E include intrahepatic dysplasia and rubella-related embryopathy.

**Useful For:** Diagnosing vitamin A deficiency and toxicity Evaluating persons with intestinal malabsorption of lipids Evaluating individuals with motor and sensory neuropathies for vitamin E deficiency Monitoring vitamin E status of premature infants requiring oxygenation

**Interpretation:** Vitamin A: The World Health Organization recommendations supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels <10.0 mcg/dL. Vitamin A values >120.0 mcg/dL suggest hypervitaminosis A and associated toxicity. Vitamin E (alpha-tocopherol): -Values that indicate need for supplementation: -Premature: <2.0 mg/L -Neonate: <2.0 mg/L -Child (3 months): <3.0 mg/L -Child (2 years): <3.0 mg/L -Adults: <3.0 mg/L -Values that indicate significant excess: -Adults: >40.0 mg/L

**Reference Values:**

**VITAMIN A (RETINOL)**
VITAMIN A (ALPHA-TOCOPHEROL)

0-17 years: 3.8-18.4 mg/L
> or =18 years: 5.5-17.0 mg/L
Significant deficiency: <3.0 mg/L
Significant excess: >40 mg/L


Clinical Information: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene (pro-vitamin A) ingested and absorbed by the intestine (carotene is converted to vitamin A by intestinal absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, where an increased incidence of death is associated with deficient vitamin A levels. Increased susceptibility is associated with vitamin A deficiency. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest >15 mg per day and children who ingest >6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheliosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg.

Useful For: Diagnosing vitamin A deficiency and toxicity Monitoring vitamin A therapy

Interpretation: The World Health Organization recommendations supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels <10.0 mcg/dL. Vitamin A values >120.0 mcg/dL suggest hypervitaminosis A and associated toxicity.

Reference Values:
0-6 years: 11.3-64.7 mcg/dL
7-12 years: 12.8-81.2 mcg/dL
13-17 years: 14.4-97.7 mcg/dL
> or =18 years: 32.5-78.0 mcg/dL

Vitamin B12 and Folate, Serum

Clinical Information: B12: Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states. Folate: The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate.(4) Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characteristically associated with macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions.(5) Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetra-hydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

Useful For: Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias Investigation of suspected folate deficiency

Interpretation: B12: Concentration of vitamin B12 <180 ng/L may cause megaloblastic anemia and/or peripheral neuropathies. Vitamin B12 concentrations <150 ng/L are considered evidence of vitamin B12 deficiency. Vitamin B12 concentrations between 150 ng/L and 300 ng/L are considered borderline. Follow-up testing for antibodies to intrinsic factor (IF) (IFBA / Intrinsic Factor Blocking Antibody, Serum) is recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies, follow-up testing of vitamin B12 tissue deficiency by measuring methylmalonic acid (MMA) (MMAS / Methylmalonic Acid [MMA], Quantitative, Serum) and/or homocysteine (HCYSP / Homocysteine, Total, Plasma) may be indicated if the patient is symptomatic. A normal serum concentration of vitamin B12 does not rule out tissue deficiency of vitamin B12. The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for MMA. If clinical symptoms suggest deficiency, measurement of MMA and homocysteine should be considered, even if serum vitamin B12 concentrations are normal. Folate: Serum folate is a relatively nonspecific test.(4) Low serum folate levels may be seen in the absence of deficiency and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results <4 mcg/L are suggestive of folate deficiency. The cut-off is based on consensus and was derived from the US NHANES III data.(5) Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Additional testing with homocysteine and MMA determinations may help distinguish between B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, both homocysteine levels and MMA levels are elevated. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:

VITAMIN B12
180-914 ng/L
**FOLATE**

> or =4.0 mcg/L

<4.0 mcg/L suggests folate deficiency


**B12 9154**

**Vitamin B12 Assay, Serum**

**Clinical Information:** Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states.

**Useful For:** Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias

**Interpretation:** A serum vitamin B12 level <180 ng/L may cause megaloblastic anemia and/or peripheral neuropathies. Vitamin B12 level <150 ng/L is considered evidence of vitamin B12 deficiency. Follow-up with tests for antibodies to intrinsic factor (IFBA / Intrinsic Factor Blocking Antibody, Serum) are recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies, follow-up testing of vitamin B12 tissue deficiency by measuring MMA (MMAS / Methylmalonic Acid [MMA], Quantitative, Serum) and/or homocysteine (HCYSP / Homocysteine, Total, Plasma) may be indicated if the patient is symptomatic. Patients with serum B12 levels between 150 and 400 ng/L are considered borderline and should be evaluated further by functional tests for vitamin B12 deficiency. The plasma homocysteine level is a good screening test. A normal level effectively excludes vitamin B12 and folate deficiency in an asymptomatic patient. However, the test is not specific and many situations can cause an increased level. In contrast, an increased serum MMA level is more specific for cellular-level B12 deficiency and is not increased by folate deficiency. Ordering ACASM / Pernicious Anemia Cascade simplifies the evaluation of B12 deficiency and will ensure that additional testing is performed in patients with a decreased vitamin B12 level: The cascade begins with serum B12 measurement. If the vitamin B12 level is <150 ng/L, intrinsic factor-blocking antibody (IFBA) testing is automatically performed. If the IFBA test is negative or indeterminate, gastrin level is evaluated. If the serum vitamin B12 level is 150 to 400 ng/L, methylmalonic acid is measured. If the methylmalonic acid is >0.40 units/L, IFBA testing is performed. If the serum vitamin B12 level is >400 ng/L, no further testing is performed. See Vitamin B12 Deficiency Evaluation in Special Instructions.

**Reference Values:**

180-914 ng/L

Vitamin B12 Binding Capacity

Reference Values:
800–2600 pg/mL

Interpretive Information: Vitamin B12 Binding Capacity
This assay measures the unsaturated binding capacity of serum for Vitamin B12.

Vitamin B12 Deficiency Panel

Reference Values:

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>NORMAL RANGE VALUES</th>
<th>B12 DEFICIENCY RANGE VALUES</th>
<th>FOLATE DEFICIENCY RANGE VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylmalonic Acid:</td>
<td>73-271 &lt;3</td>
<td>271-200,000 &gt;95</td>
<td>73-271 &lt;3</td>
</tr>
<tr>
<td>2-Methylcitric Acid:</td>
<td>60-228 &lt;3</td>
<td>228-15,000 &gt;80</td>
<td>60-228 &lt;3</td>
</tr>
<tr>
<td>Homocysteine:</td>
<td>5.1-13.9 &lt;3</td>
<td>14-500 &gt;95</td>
<td>14-250 &gt;95</td>
</tr>
<tr>
<td>Cystathionine:</td>
<td>44-342 &lt;3</td>
<td>342-4000 &gt;80</td>
<td>342-18,000 &gt;80</td>
</tr>
</tbody>
</table>

NOTE 1) Serum Methylmalonic Acid and Homocysteine are the primary metabolic tests for diagnosing and distinguishing between B12 and folate deficiency. They can be used in conjunction with the serum B12 which is usually low or low normal (<350 pg/mL) in B12 deficiency and the serum folate which is usually low or low normal (<5 ng/mL) in folate deficiency. 2-Methylcitric Acid and Cystathionine provide confirmatory evidence for such deficiencies. Homocysteine and especially Cystathionine may also be high in B6 deficiency.

NOTE 2) Elevated levels of serum metabolites will correct to normal after treatment with the appropriate vitamin but will not correct after treatment with the wrong vitamin, even in pharmacologic amounts.

NOTE 3) Any of the four metabolites can be elevated due to renal insufficiency or intravascular volume depletion. This occurs most commonly in the case of 2-Methylcitric Acid and Cystathionine. Elevated metabolite levels do not correct with B12, folate or B6 treatment unless vitamin deficiency coexists.

NOTE 4) Serum metabolite levels can be rechecked 5 to 15 days after vitamin therapy.

NOTE 5) Normal ranges 6 hours post oral Methionine load (100 mg L-Methionine/kg body wt.) are as follows: Homocysteine 16.5-45.7 umoles/Liter and Cystathionine 424-2500 nmoles/Liter. Methylmalonic Acid and 2-Methylcitric Acid do not change after a Methionine load.

Vitamin B5 (Pantothenic Acid) Bioassay

Reference Values:
Adult Reference Range
>10 Years 37 - 147 ug/L

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Pediatric Reference Range**

- **< or = 1 Year**: 3.45 to 825 ug/L
- **>1 year to 10 Years**: 3.45 to 229.2 ug/L

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**B6PRO 61064**  
**Vitamin B6 Profile (PLP and PA), Plasma**

**Clinical Information:** Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5’-phosphate esters. Due to its role as a cofactor in a number of enzymatic reactions, pyridoxal phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid (PA) are observed in cases of hypophosphatasia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

**Useful For:** Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatasia

**Interpretation:** Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results:

- If PLP is >100 mcg/L and PA is < or =30: The increased pyridoxal 5-phosphate is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphaethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine).
- If PLP is >100 mcg/L and PA is 31 to 100 mcg/L; or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L: The increased pyridoxal 5-phosphate is likely related to dietary supplementation; however a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphaethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine).
- If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30; or PLP is >100 mcg/L and PA is >100 mcg/L: The elevated pyridoxal 5-phosphate is likely due to dietary supplementation.

**Reference Values:**

- **PYRIDOXAL 5-PHOSPHATE**  
  5-50 mcg/L
- **PYRIDOXIC ACID**  
  3-30 mcg/L

**Clinical References:**

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**FBIOT 91902**  
**Vitamin B7, H (Biotin)**

**Reference Values:**

- **Pediatric**  
  <12 yrs: 57.0 â€“ 2460.2 pg/mL
- **Adult**  
  >or=12 yrs: 221.0 â€“ 3004.0 pg/mL
**Vitamin E, Serum**

**Clinical Information:** Vitamin E contributes to the normal maintenance of biomembranes the vascular system, and the nervous system, and provides antioxidant protection for vitamin A. The level of vitamin E in the plasma or serum after a 12- to 14-hour fast reflects the individual's reserve status. Currently, the understanding of the specific actions of vitamin E is very incomplete. The tocopherols (vitamin E and related fat-soluble compounds) function as antioxidants and free-radical scavengers, protecting the integrity of unsaturated lipids in the biomembranes of all cells and preserving retinol from oxidative destruction. Vitamin E is known to promote the formation of prostacyclin in endothelial cells and to inhibit the formation of thromboxanes in thrombocytes, thereby minimizing the aggregation of thrombocytes at the surface of the endothelium. Those influences on thrombocyte aggregation may be of significance in relation to risks for coronary atherosclerosis and thrombosis. Deficiency of vitamin E in children leads to reversible motor and sensory neuropathies; this problem also has been suspected in adults. Premature infants who require an oxygen-enriched atmosphere are at increased risk for bronchopulmonary dysplasia and retrolental fibroplasia; supplementation with vitamin E has been shown to lessen the severity of, and may even prevent, those problems. Deficiencies of vitamin E may arise from poor nutrition or from intestinal malabsorption. At-risk persons, especially children, include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia.

Infantile cholangiopathies that may lead to malabsorption of vitamin E include intrahepatic and extrahepatic biliary atresia, paucity of intrahepatic bile ducts, arteriohepatic dysplasia, and rubella-related embryopathy. In addition, low blood levels of vitamin E may be associated with abetalipoproteinemia, presumably as a result of a lack of the ability to form very low-density lipoproteins and chylomicrons in the intestinal absorptive cells of affected persons. Vitamin E toxicity has not been established clearly. Chronically excessive ingestion has been implicated as a cause of thrombophlebitis, although this has not been definitively verified.

**Useful For:** Evaluation of individuals with motor and sensory neuropathies Monitoring vitamin E status of premature infants requiring oxygenation Evaluation of persons with intestinal malabsorption of lipids

**Interpretation:** Values that indicate need for supplementation: -Premature: <2.0 mg/L -Neonate: <2.0 mg/L -Child (3 months): <3.0 mg/L -Child (2 years): <4.0 mg/L -Adult: <4.0 mg/L Values that indicate significant excess: -Adult: >40.0 mg/L

**Reference Values:**
- 0-17 years: 3.8-18.4 mg/L
- > or =18 years: 5.5-17.0 mg/L
- Significant deficiency: <3.0 mg/L
- Significant excess: >40 mg/L

**Clinical References:**

**Vitamin K1, Serum**

**Clinical Information:** Vitamin K1 or phylloquinone is part of a group of similar fat soluble vitamins in which the 2-methyl-1,4-naphthoquinone ring is common. Phylloquinone is found in high amounts in leafy green vegetables and some fruits (avocado, kiwi). It is a required cofactor involved in the gamma-carboxylation of glutamate residues of several proteins. Most notably, the inactive forms of the coagulation factors prothrombin (factor II), factors VII, IX, and X and protein S and protein C are converted to their active forms by the transformation of glutamate residues to gamma-carboxyglutamic acid (Gla). Other proteins such as those involved in bone metabolism, cell growth, and apoptosis also undergo this Gla transformation. Measurement of vitamin K1 (phylloquinone) in fasting serum is a strong indicator of dietary intake and status.
Useful For: Assessment of circulating vitamin K1 concentration

Interpretation: Low vitamin K1 concentrations in the serum are indicative of insufficiency and poor vitamin K1 status.

Reference Values:
> or =18 years: 0.10-2.20 ng/mL
<18 years: not established


VLTB 89190

Volatile Screen, Blood

Clinical Information: Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL.

Useful For: Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood
Quantification of the concentration of ethanol in blood which correlates with the degree of intoxication
Evaluation of toxicity to the measured volatile substances

Interpretation: Toxic concentrations: -Methanol: > or =10 mg/dL -Ethanol: > or =400 mg/dL
-Isopropanol: > or =10 mg/dL -Acetone: > or =10 mg/dL

Reference Values:
METHANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

ETHANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL

ISOPROPANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

ACETONE
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

**Volatile Screen, Chain of Custody, Blood**

**Clinical Information:** Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood. Quantification of the concentration of ethanol in blood which correlates with the degree of intoxication. Evaluation of toxicity to the measured volatile substances. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Toxic concentrations: -Methanol: \(>\text{or}=10\ \text{mg/dL}\) -Ethanol: \(>\text{or}=400\ \text{mg/dL}\) -Isopropanol: \(>\text{or}=10\ \text{mg/dL}\) -Acetone: \(>\text{or}=10\ \text{mg/dL}\)

**Reference Values:**

**METHANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: \(>\text{or}=10\ \text{mg/dL}\)

**ETHANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: \(>\text{or}=400\ \text{mg/dL}\)

**ISOPROPANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: \(>\text{or}=10\ \text{mg/dL}\)

**ACETONE**
- Not detected (Positive results are quantitated.)
- Toxic concentration: \(>\text{or}=10\ \text{mg/dL}\)

**Clinical References:**

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**Volatile Screen, Chain of Custody, Urine**

**Clinical Information:** Urine provides a medium for easy screening. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.
Useful For: Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with subsequent quantitation. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: Methanol Not detected (positive results are quantitated) Ethanol Not detected (positive results are quantitated) Isopropanol Not detected (positive results are quantitated) Acetone Not detected (positive results are quantitated)

Reference Values:
METHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ETHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

ISOPROPANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ACETONE
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL


Volatile Screen, Serum
Clinical Information: Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. -Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. -Methanol and isopropanol are highly toxic; toxicity results from ingestion (exogenous). -Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis (endogenous). It also is a metabolite of isopropanol. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. On average, the serum or plasma concentration of the alcohols is 1.2-fold higher than blood concentration. For example, the serum or plasma would contain approximately 0.10 g/dL of ethanol in a blood specimen that contains 0.08 g/dL ethanol. Due to potential variations in the serum to whole blood ratio, serum should not be used in a medico-legal context. However, in the context of medical/clinical assessment, serum or plasma may be submitted for analysis.

Useful For: Detection and quantitation of acetone, methanol, isopropanol, and ethanol in serum. Quantification of the concentration of ethanol in serum correlates with degree of intoxication. Evaluation of toxicity to the measured volatile substances.

Interpretation: Toxic concentrations: -Methanol: > or =10 mg/dL -Ethanol: > or =400 mg/dL.
-Isopropanol: > or =10 mg/dL
-Acetone: > or =10 mg/dL

Reference Values:
METHANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

ETHANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL

ISOPROPNAL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

ACETONE
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Principles of Forensic Toxicology. Edited by B Levine. Washington DC, American Association of
Clinical Chemistry, 1999

VLTU
8826

Volatile Screen, Urine
Clinical Information: Urine provides a medium for easy screening.

Useful For: Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with
subsequent quantitation

Interpretation: Methanol -Not detected (positive results are quantitated) Ethanol -Not detected
(positive results are quantitated) Isopropanol -Not detected (positive results are quantitated) Acetone -Not
detected (positive results are quantitated)

Reference Values:
METHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ETHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

ISOPROPNAL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ACETONE
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL
VWD2N von Willebrand Disease 2N (Subtype Normandy), Blood

Clinical Information: Hemophilia A (HA) and von Willebrand disease (VWD) are bleeding disorders caused by quantitative or qualitative defects in factor VIII (FVIII) or von Willebrand factor (VWF), respectively, and constitute 2 of the most common bleeding disorders. Hemophilia A is inherited as an X-linked recessive disorder while most subtypes of VWD are inherited as autosomal dominant disorders. VWF plays 2 essential roles in hemostasis. VWF mediates platelet adhesion to damaged blood vessel walls and VWF is a carrier protein for FVIII. Noncovalent binding of FVIII to VWF is necessary for normal survival of FVIII in the blood circulation. In patients with severe VWD, the circulating half-life of endogenous or infused FVIII is shortened. Mutations within the VWF gene regions encoding for the FVIII binding domain of VWF may produce a phenotype of isolated FVIII "deficiency" associated with a clinically mild-to-moderate bleeding disorder which may be misdiagnosed as HA. This mild VWD phenotype was first described in patients from the Normandy region of France, VWD Normandy (VWD Type 2N). VWD Type 2N inheritance pattern is autosomal recessive. In an international survey, VWD Normandy was detected in 58 (4.8%) of 1,198 patients previously diagnosed as having mild hemophilia A. Three VWF gene mutations (VWF Thr791Met, Arg816Trp, and Arg854Gln) accounted for 96% of patients with mutations in the FVIII binding domain of VWF.(3) Patients who are homozygous for 1 of the 3 common mutations have reduced levels of FVIII activity, whereas patients who are heterozygous typically have normal FVIII activity. However, patients who are heterozygous for 1 of the 3 common VWD Type 2N mutations may have decreased FVIII activity in the presence of a second (compound heterozygous) mutation in the VWF gene that typically results in a Type 1 or Type 3 VWD (quantitative defect). VWD Type 2N also has been associated with a more severe bleeding phenotype among patients who are homozygous for other mutations (VWF Glu24Lys) within the FVIII binding domain of VWF.(1,2) Additional studies suggest that 1.5% (3/199) to 13.8% (5/36) of patients with vWD Type 1 have a FVIII binding defect.(2,4) The diagnosis of VWD Type 2N is important for appropriate genetic counseling, because the inheritance of VWD Type 2N is autosomal recessive (as opposed to the X-linked recessive inheritance of HA). Optimal treatment or prophylaxis of bleeding requires products containing functional VWF.

Useful For: Diagnosis of von Willebrand disease (VWD) Type 2N Evaluation and genetic counseling of patients with mild-to-moderate hemophilia A with an atypical inheritance pattern Evaluation of hemophilia A patients with a shortened survival of infused factor VIII (FVIII) (not caused by a specific FVIII inhibitor) Evaluation of female patients with low FVIII activity and no prior family history of hemophilia A Evaluation of patients with Type 1 or Types 2A, 2B, or 2M VWD with FVIII activity discordantly-lower than the von Willebrand factor antigen level

Interpretation: Interpretive report will include specimen information, assay information, background information, and conclusions based on the test results. Clinical information and results of patient testing (factor VIII coagulant activity, von Willebrand factor antigen, and ristocetin cofactor activity) are useful for test interpretation.

Reference Values:
Negative

von Willebrand Factor Activity, Plasma

Clinical Information: von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments, plasma VWF and platelet VWF. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein, but does not measure platelet VWF protein. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. Patients with congenital severe type 3 von Willebrand disease (VWD) have markedly decreased or immeasurably low VWF antigen in the plasma (and in the platelets), and plasma VWF activity is very low or not detectable. Patients with types 2A and 2B variants of VWD (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen, but typically have decreased plasma VWF activity, and decreased higher molecular weight VWF multimers in the plasma. Patients with type 2M or type 2N VWD have normal levels of antigen, but either decreased VWF activity not caused by absence of higher molecular weight VWF multimers (type 2M VWD), or decreased factor VIII coagulant activity (type 2N VWD). Patients with type 1 VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and activity. Patients with acquired von Willebrand syndrome (AVWS) may have either normal or decreased plasma VWF antigen, and decreased VWF activity.

Useful For: Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtypes or differentiation of VWD from hemophilia A (Note: this activity assay is most effective when it is combined with measurement of von Willebrand factor (VWF) antigen and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting [eg, VWPR / von Willebrand Profile]) Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or VWF concentrates in patients with VWD

Interpretation: von Willebrand factor (VWF) activity is reduced in parallel with VWF antigen in von Willebrand disease (VWD), except in types 2A, 2B, and 2M, and some cases of acquired von Willebrand syndrome (AVWS) in which the VWF activity is disproportionately decreased relative to the level of VWF antigen. The VWF activity may be decreased in congenital VWD or AVWS that may be associated with a variety of disorders including monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, hypothyroidism, severe aortic stenosis, left ventricular assist device, and arteriovenous malformation. The VWF activity may be increased in association with pregnancy or estrogen use (including oral contraceptives), acute ("acute-phase reactant") or chronic inflammation, exercise or stress, liver disease, vasculitis, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Such increases in VWF activity may obscure the laboratory diagnosis of mild VWD.

Reference Values:
55-200%
Normal, full-term newborn infants may have mildly increased levels which reach adult levels by 90 days postnatal. Healthy, premature infants (30-36 weeks gestation) may have increased levels that reach adult levels by 180 days.
Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) activity than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF activity as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.

von Willebrand Factor Antigen, Plasma

Clinical Information: The von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments; plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells, and platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein, but does not reflect VWF functions or platelet VWF. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma ristocetin cofactor activity. Decreased VWF antigen may be seen in: -Congenital von Willebrand disease -Acquired VWD that may be associated with monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, and hypothyroidism Increased VWF antigen may be seen in association with: -Pregnancy and/or estrogen use -Inflammation (acute-phase reactant) -Exercise or stress -Liver disease -Vasculitis -Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Useful For: von Willebrand factor (VWF) antigen measurement is most effective when it is combined with measurement of VWF ristocetin cofactor activity and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting. Within this context, VWF antigen measurement can be useful for: -Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtype -Differentiation of VWD from hemophilia A (in conjunction with factor VIII coagulant assay) Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or VWF concentrates in patients with VWD

Interpretation: von Willebrand factor (VWF) antigen assay results generally must be used together with assays of VWF ristocetin cofactor activity and factor VIII coagulant activity, for optimum clinical utility and diagnostic efficiency. The diagnosis of von Willebrand disease (VWD) requires a combination of clinical and laboratory information. We suggest ordering VWPR / von Willebrand Profile. Patients with congenital severe type III VWD have a markedly decreased or undetectable level of VWF antigen in the plasma (and in the platelets), in addition to a plasma ristocetin cofactor activity that is very low, or not detectable. Patients with types IIA and IIB variants of VWF (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen. However, they typically have decreased plasma ristocetin cofactor activity, along with decreased higher molecular-weight VWF multimers in the plasma. Patients with types IIM or IIN VWD have normal levels of VWF antigen. In spite of this, they either have decreased vWF ristocetin cofactor activity, not caused by absence of higher molecular weight vWF multimers (type IIM VWD), or decreased factor VIII coagulant activity (type IIN VWD) Patients with type I VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and ristocetin cofactor activity. Patients with acquired VWD may have either normal or decreased plasma VWF antigen.

Reference Values:
55-200%

Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) antigen than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF antigen as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.

Children: Neonates, infants, and children have normal or mildly increased plasma VWF antigen, with respect to the adult reference range.

von Willebrand Factor Multimer Analysis, Plasma

**Clinical Information:** von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that performs 2 critical functions in hemostasis: -VWF is a ligand and mediates platelet adhesion to the subendothelial matrix at the site of vessel wall injury by binding to the constitutively active platelet receptor glycoprotein (GP)-Ib, V, IX complex, and to subendothelial matrix collagen -VWF is a carrier molecule for procoagulant factor VIII in the circulation, increasing the factor VIII half-life 5-fold. Under conditions of high shear, VWF also mediates platelet-platelet cohesion by binding to the platelet receptor GP-IIb/IIIa (integrin alpha IIb beta3) A bleeding disorder, von Willebrand disease (VWD), occurs when VWF is quantitatively deficient or qualitatively abnormal. VWD manifests clinically as easy bruising, mucocutaneous bleeding (eg, epistaxis, menorrhagia), and bleeding after trauma or surgery. VWD is the most common of the inherited bleeding disorders, and can also occur on an acquired basis. Plasma VWF consists of a series of multimers varying in size from dimers to multimers over 40 subunits (>10 million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury, and are the most hemostatically active form of VWF. Inherited VvWD has been classified into 3 types: -Type 1, typically an autosomal dominant disease, is the most common, accounting for approximately 70% of VvWD patients. It represents a quantitative deficiency of VWF of variable severity. -Type 2, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of vFWVFW . Four subtypes have been identified: 2A, 2B, 2M, and 2N. -Type 3, an autosomal recessive disorder, leads to severe disease with extremely reduced or undetectable levels of VWF, as well as very low levels of factor VIII. Acquired von Willebrand syndrome (AVWS) is associated with a number of different disease states and is caused by several different pathophysiological mechanisms, including antibody formation, proteolysis, binding to tumor cells with increased clearance, and decreased synthesis. AVWS is most frequently described in patients with dysproteinemias (including monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma, and macroglubulinemia), lymphoproliferative disorders, myeloproliferative disorders (eg, essential thrombocythemia), autoimmune diseases (eg, systemic lupus erythematosus), severe aortic stenosis, gastrointestinal angiodyplasia, and hypothyroidism.

**Useful For:** Subtyping of von Willebrand factor (VWF): -When results of complementary laboratory tests (eg, F8A / Coagulation Factor VIII Activity Assay, Plasma; VWFX / von Willebrand Activity, Plasma; and VWAG / von Willebrand Factor Antigen, Plasma) are abnormally low or discordant. -This test is primarily used to identify variants of type 2 VWF. -As an aid determining appropriate treatment

**Interpretation:** The plasma von Willebrand factor (VWF) multimer analysis is a qualitative visual assessment of the size spectrum and the banding pattern of VWF multimers. This test is used to identify variants of type 2 von Willebrand disease that have fewer of the largest multimers, have unusually large multimers, or have qualitatively abnormal "bands" that indicate an abnormal VWF structure.

**Reference Values:**
An interpretive report will be provided.

von Willebrand Profile

Clinical Information: von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma. VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic "plug" and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor. VWF circulates in the blood in 2 distinct compartments. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high- molecular-weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory with the VWF activity assay, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers and is useful as a reflexive test for subtyping von Willebrand disease (VWD). Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within each individual over time and also with blood type (normal type "O" individuals may have VWF lower than normals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. VWF antigen measurement assesses the mass of plasma VWF protein but does not reflect VWF functions or platelet VWF. The function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal, including epistaxis, menorrhagia, gastrointestinal bleeding, and ease of bruising, but surgical or posttraumatic bleeding can also occur. Subtypes of inherited VWD are: Type 1 VWD: VWF plasma levels (antigen and activity) typically are both concordantly reduced in Type 1 VWD. Because of this reduction, the level of coagulation factor VIII is often secondarily reduced also. Type 1 VWD is the most common VWD variation, representing 70% to 80% of clinical VWD. It is typically inherited in autosomal dominance fashion, although recessively inherited VWD also occurs (eg, Type 3 VWD). Clinical severity ranges from mild or minimal to a moderately severe bleeding diathesis and tends to correlate most closely with VWF activity. Severe Type 1 disease is also called Type 3 VWD, but the distinction between the 2 may sometimes be difficult. Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of Type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of Types 2A and 2B, but are normal in Type 2M or 2N. VWF activity is decreased in Types 2A, 2B, and 2M and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (typically 5%-30% of mean normal), with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomally inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A). Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from Type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen not due to loss of HMW multimers. One variant of Type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Type 3 VWD: VWF is absent or markedly decreased in Type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal, with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected.
Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.

**Useful For:** Detection of deficiency or abnormality of von Willebrand factor and related deficiency of factor VIII coagulant activity Subtyping von Willebrand disease as Type 1 (most common), Type 2 variants (less common), or Type 3 (rare)

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**

**FACTOR VIII ACTIVITY**
55-200%

**von WILLEBRAND FACTOR ACTIVITY**
55-200%

**von WILLEBRAND FACTOR ANTIGEN**
55-200%

**Clinical References:**

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**Voriconazole, Serum**

**Clinical Information:** Voriconazole (Vfend) is an antifungal agent approved for treatment of invasive aspergillosis and candidemia/candidiasis, as well as for salvage therapy for infections in patients refractory to or intolerant of other antifungal therapy. The drug inhibits the fungal enzyme 14a-sterol demethylase, a critical step in ergosterol biosynthesis. Voriconazole is metabolized in the liver primarily by CYP2C19; CYP2C9 and CYP3A4 play limited roles. The primary metabolite is voriconazole N-oxide, which has no antifungal activity. Drug clearance is primarily dependent on hepatic metabolism. The pharmacokinetics of voriconazole is highly variable and nonlinear, which results in an increased dose leading to a greater than proportional increase in serum concentration. The bioavailability of oral voriconazole is >95%. Approximately 60% of the drug in serum is protein bound. Voriconazole has a volume of distribution of 4.6 L/kg. Most (80%) of the drug is excreted in the urine, exclusively as metabolites. Adverse effects of voriconazole include visual disturbances, skin rashes, and elevated liver enzyme levels.

**Useful For:** Monitoring trough levels of voriconazole is suggested in individuals with reduced liver function, individuals with CYP2C19 polymorphisms associated with poor metabolic function, patients taking other medications that affect CYP2C19 activity, and in patients experiencing potential toxicity. Monitoring trough levels may be reasonable in patients who are not responding optimally or have drug interactions that may decrease voriconazole levels, or to ensure adequate oral absorption.

**Interpretation:** Trough levels >6 mcg/mL (and especially >10 mcg/mL) have been associated with toxicity in several reports. Trough levels <1 mcg/mL have been associated with suboptimal response in several reports.

**Reference Values:**
1.0-5.5 mcg/mL

Trough level (ie, immediately before next dose) monitoring is recommended.

**Clinical References:**
**Wall Eyed Pike (Sander vitreus)(Stizostedium vitreum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**

<0.35 kU/L

**Walnut Food (Juglans spp) IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Walnut Tree, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. Testing also may be useful to define allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Reference Values:**

Class IgE kU/L Interpretation

- 0 Negative
- 1 0.35-0.69 Equivocal

**Walnut-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
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<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Clinical Information:** Warfarin is a Coumarin-based drug commonly utilized in anticoagulation therapy to prevent thrombosis due to inherited and acquired hemostatic disorders. The drug is also used in a number of other medical conditions and treatments including atrial fibrillation and hip replacement surgery. Warfarin acts by interfering with the metabolism of vitamin K, which is necessary for production of key coagulation factors. Warfarin inhibits vitamin K recycling by blocking its metabolism at the vitamin K-epoxide intermediate, thereby decreasing the amount of available vitamin K. Warfarin has a narrow therapeutic window; under medicating increases the risk for thrombosis and overmedicating increases the risk for cerebrovascular accidents. Warfarin therapy has one of the highest rates of severe adverse drug reactions. Warfarin is dosed using nongenetic factors including gender, weight, and age, and is monitored by coagulation testing in order to maintain the international normalized ratio (INR) within specific limits. However, warfarin metabolism is highly variable and dependent upon genetic factors. Variants within 2 genes are known to affect the metabolism of warfarin and the dose needed to maintain the correct serum drug level and degree of anticoagulation. The CYP2C9 gene encodes the cytochrome P450 2C9 (CYP2C9) enzyme that primarily metabolizes the more active isomer of warfarin (S-warfarin) to inactive products. Some CYP2C9 variants result in decreased enzymatic activity and may lead to increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. The second gene (VKORC1) encodes vitamin K epoxide reductase complex subunit-1 (VKORC1), a small transmembrane protein of the endoplasmic reticulum that is part of the vitamin K cycle and the target of warfarin therapy. Vitamin K epoxide, a by-product of the carboxylation of blood coagulation factors, is reduced to vitamin K by VKORC1. A VKORC1 promoter variant leads to decreased expression of the gene, resulting in reduced availability of vitamin K. This may cause increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. Thus, the presence of CYP2C9 and/or VKORC1 variants may result in the need for a reduced warfarin dose and more careful monitoring in order to maintain the target INR. CYP2C9: CYP2C9 metabolizes a wide variety of drugs including warfarin and phenytoin. A number of specific CYP2C9 variants result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in this assay and their effect on the activity of the enzyme: CYP2C9 Allele cDNA Nucleotide Change Effect on Enzyme Metabolism

<table>
<thead>
<tr>
<th>Allele</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 None (wild type)</td>
<td>Extensive metabolizer (normal)</td>
</tr>
<tr>
<td>*2 430C-&gt;T</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>*3 1075A-&gt;C</td>
<td>Minimal activity</td>
</tr>
<tr>
<td>*4 1076T-&gt;C</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>*5 1080C-&gt;G</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>*6 818delA</td>
<td>No activity</td>
</tr>
<tr>
<td>*8 449G-&gt;A</td>
<td>Substrate specific</td>
</tr>
<tr>
<td>*9 752A-&gt;G</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>*11 1003C-&gt;T</td>
<td>Reduced activity</td>
</tr>
</tbody>
</table>

VKORC1: The c.-1639A variant is located in the second nucleotide of an E-Box (CANNTG) and its presence disrupts the consensus sequence, reducing promoter activity. In vitro experiments show a 44% higher transcription level of the G versus the A allele. The c.-1639 G>A nucleotide change results in decreased gene expression and reduced enzyme activity. Warfarin dosing may require adjustment dependent on CYP2C9 and VKORC1 genotype and predicted phenotype. Patients who are CYP2C9 poor metabolizers (reduced activity) may benefit from warfarin dose reductions or by being switched to other comparable drugs that are not metabolized primarily by CYP2C9. Refer to the drug label for additional information, available at:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=558b7a0d-5490-4c1b-802e-3ab3f1e760

**Useful For:** Identifying patients who may require warfarin dosing adjustments including: -Patients who have previously been prescribed warfarin and have required multiple dosing adjustments to maintain the international normalized ratio in the target range -Patients with a history of thrombosis or bleeding when taking warfarin -Patients being started on a first prescription for warfarin

**Interpretation:** An interpretive report will be provided that includes assay information, genotype, and an interpretation indicating the patient's predicted warfarin sensitivity. The CYP2C9 genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee. Individuals without a detectable gene alteration will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C9*1/*1. Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. The c.-1639A variant reduces VKORC1 expression. The VKORC1 GA or AA genotype leads to a significant decrease in VKORC1 expression compared with the GG genotype. For additional information regarding
pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Individuals who have variants in both the VKORC1 promoter (GA or AA) and also in CYP2C9 should receive a reduced dose of warfarin and more frequent monitoring of international normalized ratio (INR) to maintain the INR in the target range; dosing adjustments are required when variants in both genes are present. Drug-drug interactions and drug/metabolite inhibition must be considered in the case of intermediate metabolism. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.


Warfarin Sensitivity Genotype by Sequence Analysis, Saliva

Clinical Information: Warfarin is a Coumadin-based drug commonly utilized in anticoagulation therapy to prevent thrombosis due to inherited and acquired hemostatic disorders. The drug is also used in a number of other medical conditions and treatments including atrial fibrillation and hip replacement surgery. Warfarin acts by interfering with the metabolism of vitamin K, which is necessary for production of key coagulation factors. Warfarin inhibits vitamin K recycling by blocking its metabolism at the vitamin K-epoxide intermediate, thereby decreasing the amount of available vitamin K. Warfarin has a narrow therapeutic window; under medicating increases the risk for thrombosis and overmedicating increases the risk for cerebrovascular accidents. Warfarin therapy has one of the highest rates of severe adverse drug reactions. Warfarin is dosed using nongenetic factors including gender, weight, and age, and is monitored by coagulation testing in order to maintain the international normalized ratio (INR) within specific limits. However, warfarin metabolism is highly variable and dependent upon genetic factors. Variants within 2 genes are known to affect the metabolism of warfarin and the dose needed to maintain the correct serum drug level and degree of anticoagulation. The CYP2C9 gene encodes the cytochrome P450 2C9 (CYP2C9) enzyme that primarily metabolizes the more active isomer of warfarin (S-warfarin) to inactive products. Some CYP2C9 variants result in decreased enzymatic activity and may lead to increases in serum warfarin and overmedicating, driving the INR above the therapeutic target level. The second gene (VKORC1) encodes vitamin K-epoxide reductase complex subunit-1 (VKORC1), a small transmembrane protein of the endoplasmic reticulum that is part of the vitamin K cycle and the target of warfarin therapy. (1) Vitamin K epoxide, a by-product of the carboxylation of blood coagulation factors, is reduced to vitamin K by VKORC1. A VKORC1 promoter variant leads to decreased expression of the gene, resulting in reduced availability of vitamin K. This may cause increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. Thus, the presence of CYP2C9 and/or VKORC1 variants may result in the need for a reduced warfarin dose and more careful monitoring in order to maintain the target INR. CYP2C9: CYP2C9 metabolizes a wide variety of drugs including warfarin and phenytoin. A number of specific CYP2C9 variants result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in this assay and their effect on the activity of the enzyme: CYP2C9 Allele cDNA Nucleotide Change Effect on Enzyme Metabolism *1 None (wild type) Extensive metabolizer (normal) *2 430C->T Reduced activity *3 1075A->C Minimal activity *4 1076T->C Reduced activity *5 1080C->G Reduced activity *6 818delA No activity *8 449G->A Substrate specific *9 752A->G Reduced activity *11 1003-C>T Reduced activity VKORC1: The c.-1639 promoter variant is located in the second nucleotide of an E-Box (CANNTG) and its presence...
disrupts the consensus sequence, reducing promoter activity. In vitro experiments show a 44% higher transcription level of the G versus the A allele.(1) The c.-1639 G->A nucleotide change results in decreased gene expression and reduced enzyme activity. Warfarin dosing may require adjustment dependent on CYP2C9 and VKORC1 genotype and predicted phenotype. Patients who are CYP2C9 poor metabolizers (reduced activity) may benefit from warfarin dose reductions or by being switched to other comparable drugs that are not metabolized primarily by CYP2C9. Refer to the drug label for additional information, available at:
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=558b7a0d-5490-4c1b-802e-3ab3f1efe760

**Useful For:** Identifying patients who may require warfarin dosing adjustments(2,3) including: -Patients who have previously been prescribed warfarin and have required multiple dosing adjustments to maintain the international normalized ratio in the target range -Patients with a history of thrombosis or bleeding when taking warfarin -Patients being started on a first prescription for warfarin Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report will be provided that includes assay information, genotype, and an interpretation indicating the patientâ€™s predicted warfarin sensitivity. The CYP2C9 genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Human Cytochrome P450 (CYP) Allele Nomenclature Database Committee.(4) Individuals without a detectable gene alteration will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C9*1/*1. Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. The c.-1639A variant reduces VKORC1 expression. The VKORC1 GA or AA genotype leads to a significant decrease in VKORC1 expression compared with the GG genotype. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Individuals who have variants in both the VKORC1 promoter (GA or AA) and also in CYP2C9 should receive a reduced dose of warfarin and more frequent monitoring of international normalized ratio (INR) to maintain the INR in the target range; dosing adjustments are required when variants in both genes are present. Drug-drug interactions and drug/metabolite inhibition must be considered in the case of intermediate metabolism. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

**Reference Values:**
An interpretive report will be provided.


**Warfarin, Serum**

**Clinical Information:** Warfarin (Coumadin) is an anticoagulant that acts by antagonizing the action of vitamin K resulting in the same coagulation abnormalities produced by vitamin K deficiency. Warfarin reduces the levels of prothrombin and factors VII, IX, and X, thereby prolonging the prothrombin and partial thromboplastin times. Warfarin produces its anticoagulant effect within 36 to 72 hours of initiating therapy, and the duration of action may persist for 4 to 5 days following withdrawal of drug. Warfarin circulates almost completely bound to albumin (>98%), and its half-life ranges from 20 to 60 hours. Abnormal bleeding is the chief complication of overdose.
Useful For: Monitoring patients whose prothrombin time is inconsistent with the prescribed warfarin dose, particularly when failure to comply or surreptitious drug use is suspected. Note: This test is not useful for evaluation of the patient with prolonged bleeding time suspected of exposure to rat poisons.

Interpretation: Therapeutic concentration: 2.0 to 5.0 mcg/mL Toxic concentration: > or =10.0 mcg/mL

Reference Values:
Therapeutic concentration: 2.0-5.0 mcg/mL
Toxic concentration: > or =10.0 mcg/mL


Wasp Venom, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tr>
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<th>IgE kU/L</th>
<th>Interpretation</th>
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<tr>
<td>0</td>
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<tr>
<td>2</td>
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<td>Positive</td>
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<tr>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Watermelon IgG

**Interpretation:** mcg/mL of IgG
Lower Limit of Quantitation: 2.0
Upper Limit of Quantitation: 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Watermelon, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

### Weed Panel # 1

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


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### Weed Panel # 2

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
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</tr>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*


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**WEED4 Weed Panel # 4**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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<td>3.50-17.4</td>
<td>Positive</td>
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<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
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</tbody>
</table>

West Nile CSF Interpretation

Reference Values:
Only orderable as part of a profile. For more information see WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

West Nile Serum Interpretation

Reference Values:
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

West Nile Virus (WNV) Antibody, IgG and IgM, Serum

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but occasionally infects horses and humans. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) In 2002, a total of 3,389 human cases of WNV infection were reported from 37 states (794 cases in Illinois); 2,354 (69%) presented with meningoencephalitis, 704 (21%) had West Nile fever, and 331 (10%) had an unspecified illness.(2) Overall, the WNV epidemic in the United States was the largest arboviral meningoencephalitis outbreak documented in the Western hemisphere. In addition, 33 cases of probable WNV infection occurred among persons who had received blood components in the month before illness onset.(3) Most people who are infected with WNV will not have any type of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) result in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV / West Nile Virus [WNV] RNA Detection by Rapid PCR) can detect WNV RNA in specimens from patients with WNV infection when specific antibodies to the virus are not present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Laboratory diagnosis of acute phase infection with West Nile virus

Interpretation: IgM: Presence of specific IgM class antibodies in a serum specimen is consistent with acute-phase infection with West Nile virus (WNV). By the eighth day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months after onset of illness, in some cases it will be detectable for 12 months or longer. Absence of IgM class antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (eg, before 8 days postinfection) may be negative for IgM-specific antibodies to WNV. If WNV infection is suspected, a second specimen drawn approximately 14 days postinfection should be tested. IgG: Presence of specific IgG class antibodies in a serum specimen indicates infection with WNV sometime in the past. By 3 weeks postinfection, virtually all infected persons should have
developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum.

Reference Values:
IgG: negative
IgM: negative
Reference values apply to all ages.


West Nile Virus (WNV) Antibody, IgG and IgM, Spinal Fluid

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but occasionally infects horses and humans. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) In 2002, a total of 3,389 human cases of WNV infection were reported from 37 states (794 cases in Illinois); 2,354 (69%) presented with meningoencephalitis, 704 (21%) had West Nile fever, and 331 (10%) had an unspecified illness.(2) Overall, the WNV epidemic in the United States was the largest arboviral meningoencephalitis outbreak documented in the Western hemisphere. In addition, 33 cases of probable WNV infection occurred among persons who had received blood components in the month before illness onset.(3) Most people who are infected with WNV will not have any type of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) result in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis of WNV is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens from patients. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months after onset of illness, in some cases it will be detectable for 12 months or longer. By 3 weeks postinfection, virtually all infected persons should have developed serum IgG antibodies to WNV. The specific identification of WNV by detection of IgM in cerebrospinal fluid (CSF) is the recommended test to document central nervous system disease, but this test may be falsely negative in CSF collected <8 days after the onset of symptoms. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can detect WNV RNA in specimens from patients with WNV infection when specific antibodies to the virus are not present. However, the likelihood of detection is relatively low as PCR sensitivity in CSF is approximately 55%, and in blood, about 10% in patients with known WNV infection.

Useful For: Preferred test for the laboratory diagnosis of West Nile virus meningitis or encephalitis

Interpretation: IgM: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum. A negative result may indicate the absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-specific antibodies to WNV. If WNV central nervous system (CNS) infection is suspected, a second specimen
should be collected in 1 to 2 weeks and tested. IgG: A positive result is consistent with CNS infection with WNV sometime in the past.

**Reference Values:**
IgG: negative
  IgM: negative
Reference values apply to all ages.

**Clinical References:**

---

**West Nile Virus (WNV), Molecular Detection, PCR, Plasma**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds, but occasionally infects horses and humans. Until the virus infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern hemisphere, with a wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms including headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) result in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum or cerebrospinal fluid (CSF) specimens (WNV / West Nile Virus [WNV] Antibody, IgG and IgM, Serum or WNVC / West Nile Virus [WNV] Antibody, IgG and IgM, Spinal Fluid). The specific identification of WNV by detection of IgM in CSF is the recommended test to document central nervous system disease, but this test may be falsely negative in CSF collected <8 days after the onset of symptoms. Alternatively, experiences in nucleic acid testing for WNV RNA in blood prior to transfusion have indicated that PCR can detect viremic target RNA from patients with known West Nile infection when specific antibodies to the virus are not present (ie, from 2-8 days after onset of symptoms).(4,5)

**Useful For:** Rapid testing for West Nile virus (WNV) RNA As an adjunct in the diagnosis of early WNV virus infection

**Interpretation:** The likelihood of detection of West Nile virus RNA by PCR is relatively low. In cerebrospinal fluid, the clinical sensitivity is approximately 55%, and in blood, about 10%. Specificity of the assay in either matrix is approximately 100%.(6)

**Reference Values:**
Negative

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**West Nile Virus Antibody, IgG and IgM, Serum**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is
estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Laboratory diagnosis of infection with West Nile virus

**Interpretation:**
- **IgG:** The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (eg, before 8 to 10 days post-infection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

**Reference Values:**
- **IgG:** Negative
- **IgM:** Negative

Reference values apply to all ages.

**Clinical References:**

**West Nile Virus Antibody, IgG and IgM, Spinal Fluid**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe. Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death. Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can
detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Laboratory diagnosis of infection with West Nile virus

**Interpretation:** IgM: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested. IgG: A positive result is consistent with CNS infection with WNV sometime in the past. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

**Reference Values:**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Serum</th>
<th>Spinal Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Negative</td>
<td>Reference values apply to all ages.</td>
</tr>
<tr>
<td>IgM</td>
<td>Negative</td>
<td>Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:**


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**WNGS**

West Nile Virus Antibody, IgG, Serum

**Reference Values:**

Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

**WNGC**

West Nile Virus Antibody, IgG, Spinal Fluid

**Reference Values:**

Only orderable as part of a profile. For more information see WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

**WNMS**

West Nile Virus Antibody, IgM, Serum

**Reference Values:**

Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

**WNMC**

West Nile Virus Antibody, IgM, Spinal Fluid

**Reference Values:**

Only orderable as part of a profile. For more information see WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.
**West Nile Virus, Molecular Detection, PCR**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds, but occasionally infects horses and humans. Until the virus infection was recognized in 1999 in birds in New York City, WNV had been detected only in the Eastern hemisphere, with a wide distribution in Africa, Asia, the Middle East, and Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms including headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) result in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. PCR testing can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood from patients with known WNV infection.

**Useful For:** Rapid testing for West Nile virus (WNV) RNA An adjunctive test to serology for detection of early WNV infection

**Interpretation:** A positive result indicates the presence of West Nile virus (WNV) RNA and is consistent with early WNV infection.

**Reference Values:**
Negative


**Western Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid**

**Clinical Information:** The virus that causes western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.
Useful For: Aiding the diagnosis of Western equine encephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.


Western Equine Encephalitis Antibody, IgG and IgM, Serum

Clinical Information: The virus that causes western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile central nervous system disease from an endemic area. Infants are highly susceptible to central nervous system disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults.

Useful For: Aiding the diagnosis of Western equine encephalitis

Interpretation: In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG $>$ or =1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Eastern equine encephalitis (WEE) and eastern equine encephalitis (EEE) antigens will show a noticeable cross-reactivity. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age: WEE tends to produce the most severe clinical infections in young persons. Infection in males is primarily due to working conditions and sports activity taking place where the vector is present.

Reference Values:
IgG: <1:10
IgM: <1:10

Western Ragweed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Wheat IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Current as of July 8, 2016 11:28 am CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Reference Values:
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FWHG4 57570**

**Wheat IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**
<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**WHT 82686**

**Wheat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Whey IgG

Interpretation: mcg/mL of IgG

Lower Limit of Quantitation 2.0
Upper Limit of Quantitation 200

Reference Values:

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Whey, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
ASHW 82730

White Ash, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

White Bean, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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White Faced Hornet Venom, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
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Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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White Hickory, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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### Clinical References:


### White Pine, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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White Potato, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Whitefish IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very
Wild Rye Grass, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Wild Silk, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for...
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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Reference values apply to all ages.

development of connective tissue, including the heart, but have other features of WS.

**Useful For:** Establishing a diagnosis of Williams syndrome Detecting cryptic rearrangements involving 7q11.23 that are not demonstrated by conventional chromosome studies

**Interpretation:** The use of high-resolution chromosome studies and FISH for Williams syndrome chromosome region should diagnose about 96% of Williams syndrome patients and, at the same time, identify any other chromosome anomalies.

**Reference Values:**
An interpretive report will be provided.


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**Willow, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders
Wilson Disease, Full Gene Analysis

Clinical Information: Wilson disease (WD) is an autosomal recessive disorder that results from the body's inability to excrete excess copper. Typically, the liver releases excess copper into the bile. Individuals with WD lack the necessary enzyme that facilitates clearance of copper from the liver to bile. As a result, copper accumulates first in the liver and gradually in other organs. The brain, kidneys, bones, and corneas can also be affected. WD affects approximately 1 in 30,000 people worldwide, with a carrier frequency of approximately 1 in 90 individuals. The primary clinical manifestations of WD are hepatic and neurologic. Hepatic disease can be quite variable, ranging from hepatomegaly to other nonspecific symptoms that mimic viral hepatitis to severe liver damage, such as cirrhosis. Neurologic symptoms of WD can include poor fine-motor coordination, ataxia, and dysphagia. Psychiatric manifestations are reported in approximately 20% of individuals with WD. A characteristic ophthalmologic finding is the Kayser-Fleischer ring. Individuals with WD typically begin to show symptoms of liver dysfunction or neurologic disease in the first or second decade of life. If not treated, WD can cause liver failure, severe brain damage, and even death. A variety of laboratory tests are recommended in the initial evaluation for WD. In approximately 95% of cases, serum ceruloplasmin is below normal. Additionally, patients with WD show decreased copper in serum, increased copper in urine, and significantly elevated copper on liver biopsy. While liver biopsy is not recommended as a first-tier screening test for WD, it can be useful to help interpret discrepant biochemical or molecular results. The other tests should be performed prior to sequence analysis of the ATP7B gene, the gene responsible for WD. More than 300 disease-causing mutations have been identified in the ATP7B gene. Most mutations are family-specific with the exception of the H1069Q mutation, which accounts for >50% of identified disease alleles in the Northern European Caucasian population. See Wilson Disease Testing Algorithm in Special Instructions for additional information.

Useful For: Diagnostic confirmation of Wilson disease

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Wingscale (Atriplex Canescens) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

Wolf-Hirschhorn Syndrome, 4p16.3 Deletion, FISH

Clinical Information: This test is appropriate for individuals with clinical features suggestive of Wolf-Hirschhorn syndrome. Wolf-Hirschhorn syndrome is associated with a deletion on the short arm of
chromosome 4 (4p16.3). The syndrome is manifested by pre- and postnatal growth retardation and severe hypotonia (decreased muscle tone). The common major birth defects include microcephaly (small head), cleft lip and/or palate, and severe heart malformations. Facial features include cranial asymmetry, prominent forehead, hemangioma, preauricular pits or tags, coloboma of the iris or other eye malformations, hypertelorism (wide-spaced eyes), micrognathia (small jaw), and a long neck. Many other birth defects have been seen including brain and kidney malformations, hernias, abnormal external and internal genitalia, simian crease (single palmar crease), and cutis aplasia (failure of skin development) of the scalp. Most affected individuals are stillborn or die in the first year, although survival beyond age 20 has been reported. Mental retardation is profound, and survivors have seizures and severe hypotonia. FISH studies are highly specific and do not exclude other chromosome abnormalities. For this reason we recommend that patients suspected of having Wolf-Hirschhorn syndrome also have conventional chromosome studies (CHRCB / Chromosomes Analysis, Congenital Disorders, Blood) performed to rule out other chromosome abnormalities or translocations.

**Useful For:** Establishing a diagnosis of Wolf-Hirschhorn syndrome Detecting cryptic rearrangements involving 4p16.3 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern (2 signals) in each metaphase is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe. This is consistent with a diagnosis of Wolf-Hirschhorn syndrome (4p16.3 deletion).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Wormwood, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
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**BUCCF**

### X and Y Aneuploidy Detection, Buccal Smear, FISH

**Clinical Information:** Aneuploidy of the sex chromosomes is common among recognized congenital syndromes. For example, the majority (80%) of individuals with Klinefelter syndrome have 2 X chromosomes and 1 Y chromosome; the remainder are mosaics or variants. Individuals with Turner syndrome have a single X chromosome in 55% of cases; the remaining 45% are either variants or mosaics. Conventional cytogenetic analysis should be performed for confirmation, especially when the results are abnormal. Structural abnormalities of X and Y chromosomes will be missed by this technique, as will low-level mosaicism. This test can detect between 50% to 70% of Turner syndrome cases (only those caused by complete lack of 1 sex chromosome [45,X] or high-level mosaicism for a 45,X). Congenital blood chromosome analysis (CMS / Chromosome Analysis, for Congenital Disorders, Blood) should always be performed for Turner syndrome. The test does not rule out numeric or structural cytogenetic anomalies involving chromosomes other than X and Y.

**Useful For:** Diagnosis of mosaic sex chromosome aneuploidy as a supplement to conventional chromosome studies in patients with normal or uncertain chromosome results or when an alternative tissue needs to be studied.

**Interpretation:** Specimens that contain >5% cells with a signal pattern other than XX in females and XY in males have a very high likelihood of having a clone of cells with an abnormal complement of sex chromosomes. Specimens with <5% of cells with a signal pattern other than XX in females and XY in males most likely do not have a clone of cells with an abnormal complement of sex chromosomes, but the presence of an abnormal clone of cells is not completely ruled out.

**Reference Values:**
An interpretive report will be provided.


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**XISTF**

### X-Inactivation (XIST), Xq13.2 Deletion, FISH

**Clinical Information:** Turner syndrome is characterized by ovarian hypofunction, short stature, loose skin folds at the back of the neck, and cubitus valgus (elbow deformity) and results from complete or partial monosomy of the X chromosome. Phenotypic expression of Turner syndrome patients is largely dependent on the patient's karyotype and identification of sex chromosomes mosaicism plays a key role in clinical management. In mosaicism, 2 or more populations of cells with different karyotypes are present (eg, 45,X/46,XX). Additionally, mental retardation is more common in patients with a small ring...
chromosome derived from an X chromosome with a deletion of the X-inactivation center (XIST) at Xq13.2. FISH studies are highly specific and do not exclude other chromosome abnormalities, we recommend that patients suspected of having Turner syndrome also have conventional chromosome studies (CHRCB / Chromosomes, Congenital, Blood) performed to rule out other chromosome abnormalities or translocations.

**Useful For:** Evaluation of marker chromosomes derived from chromosome X

**Interpretation:** Any individual with a normal signal pattern (signal on each normal X homolog) in each metaphase is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the XIST critical region will be reported as having a deletion of the regions by this probe.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**XALDZ**

**X-Linked Adrenoleukodystrophy, Full Gene Analysis**

**Clinical Information:** X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease characterized by magnetic resonance imaging (MRI) findings in the white matter, adrenocortical insufficiency, and abnormal plasma concentrations of very long chain fatty acids. The phenotypic expression of X-ALD varies widely. The phenotypes can be subdivided into 3 main categories: childhood cerebral form, adrenomyeloneuropathy (AMN), and Addison disease only. The childhood cerebral form has onset of symptoms between ages 4 and 8, beginning with attention deficit hyperactivity disorder-like symptoms with progressive cognitive, behavior, vision, hearing, and motor deterioration. AMN usually presents in males in their late twenties as progressive paraparesis, sexual dysfunction, sphincter disturbances, and abnormalities in adrenocortical function. The Addison only phenotype typically presents by age 7.5 with adrenocortical insufficiency without significant neurological involvement. Most of these patients eventually develop AMN. Some female carriers may experience mild AMN symptoms with a later age of onset. The phenotype cannot be predicted by very long chain fatty acids (VLCFA) plasma concentration or by the nature of the mutation. The same mutation can be associated with each of the known phenotypes. Different phenotypes often occur within a family. POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum testing is the preferred first-tier screening method for X-ALD. This is abnormal in 99% of affected males and 85% of carrier females. Sequencing of the ABCD1 gene is available to confirm the diagnosis of X-ALD, improve carrier detection, and assist with prenatal diagnosis.

**Useful For:** Confirming a diagnosis of X-linked adrenoleukodystrophy Identifying a mutation in the ABCD1 gene

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
X-Linked Hyper IgM Syndrome, Blood

**Clinical Information:** CD154 (CD40 ligand: CD40L) is required for the interaction of T cells and B cells as part of the normal adaptive immune response. Activation of T cells leads to the expression of the CD40L molecule on the cell surface. CD40L binds the CD40 receptor that is always present on B cells, monocytes, and macrophages (regardless of environmental conditions). This interaction of CD40L with CD40 is important in B-cell proliferation, differentiation, and class-switch recombination (isotype class-switching). Patients with X-linked hyper-IgM (XL-HIGM) syndrome have defective CD40L expression on their activated helper CD4 T cells.(1,2) This leads to defective B-cell responses and the absence of immunoglobulin class-switching. These features are typified in these patients by a profound reduction or absence of isotype class-switched memory B cells (CD19+CD27+IgM-IgD-) with low or absent secreted IgG and IgA, and normal or elevated serum IgM levels.(1,2) Due to the impairment of T-cell function and macrophage activation, XL-HIGM patients are particularly prone to opportunistic infections with Pneumocystis jiroveci, Cryptosporidium, and Toxoplasma gondii.(1) To date, more than 100 unique mutations of CD40LG, the gene that encodes CD40L, have been described, affecting the intracellular, transmembrane and, more commonly, extracellular domain containing the CD40-binding region. A defect in surface expression of CD40L on activated CD4 T cells can be demonstrated using an anti-CD40L antibody and flow cytometry.(3,4) Since certain CD40LG mutations can maintain surface protein expression, albeit with loss of function, it is important to also evaluate CD40L-binding capacity to eliminate the possibility of false-negative results. A soluble recombinant, chimeric receptor protein, CD40-ulN, is incorporated into the assay, which assesses CD40L function by determining receptor-binding activity. Approximately 20% of XL-HIGM patients have activated CD4 T cells with normal surface expression of CD40L, but aberrant function.(4) XL-HIGM is a severe type of primary immunodeficiency that affects males, and most patients are diagnosed within a few months to the first year of life. Females are typically carriers and asymptomatic. Consequently, this test is only indicated in young males (<10 years of age) or, to identify carriers, in females of child-bearing age (<45 years).

**Useful For:** Screening for X-linked hyper-IgM (XL-HIGM) or CD40L deficiency, primarily in male patients <10 years of age. Ascertain XL-HIGM carrier status in females of child-bearing age <45 years of age.

**Interpretation:** This is a qualitative assay; CD40L-protein expression and function is reported as present or absent. Absence of CD40L-protein expression and function is consistent with X-linked hyper-IgM (XL-HIGM). In females, the presence of 2 populations-normal and abnormal-is consistent with carrier status. Most patients (80-90%) with XL-HIGM have absent or significantly reduced CD40L expression on their activated CD4 T cells. Patients with normal CD40L expression, but abnormal function, show an absence of binding with soluble chimeric CD40-ulN antibody, substantiating a diagnosis of XL-HIGM. Females who are carriers for this disease will show a typical bimodal pattern of CD40L expression, with 50% of the T cells lacking any CD40L expression. In the case of aberrant protein function, a similar profile will be obtained with the CD40-ulN antibody. CD69 is a marker for T-cell activation and serves as a positive control; in the absence of induced CD69 expression on T cells, the presence of XL-HIGM cannot be assessed.

**Reference Values:**

Present

**Clinical References:**

Xanthine and Hypoxanthine, 24 Hour, Urine

**Current as of July 8, 2016 11:28 am CDT**

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Clinical Information:** Xanthine and hypoxanthine are the direct precursors of uric acid, the end product of purine metabolism. Two inborn errors of metabolism are characterized by elevated excretion of xanthine and hypoxanthine. Patients with isolated xanthine dehydrogenase (XDH, xanthine oxidase) deficiency may remain asymptomatic, but nephrolithiasis, due to the insolubility of xanthine, may occur at any age. Some patients also develop a myopathy with crystalline xanthine deposits in muscle. Combined deficiency of XDH and the related enzyme sulfite oxidase (SO) is also characterized by nephrolithiasis, but more prominently by the symptoms of SO deficiency (isolated SO deficiency also occurs) including neonatal seizures, myoclonus, lens dislocation, and severe mental retardation. This form of xanthinuria is caused by molybdenum cofactor deficiency, which is required for the activity of both oxidases. Elevations of xanthine and hypoxanthine and abnormally low levels of uric acid are found in both disorders, while in patients with XDH/SO deficiency sulfites and sulfur-containing metabolites (S-sulfocysteine, thiosulfate, taurine) also accumulate. Analysis of xanthine and hypoxanthine alone, allows the diagnosis of xanthinuria, is helpful for the evaluation of low serum and/or urine uric acid concentrations, and for the evaluation of allopurinol (a xanthine oxidase inhibitor) treatment in hyperuricemic disorders (eg, Lesch-Nyhan syndrome).

**Useful For:** Diagnosis and confirmation of xanthinuria Evaluation of low serum or urine uric acids Evaluation of allopurinol treatment in hyperuricemic disorders (eg, Lesch-Nyhan syndrome)

**Interpretation:** Abnormal concentrations of xanthine and hypoxanthine will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name and phone number of contacts who may provide these studies at the Mayo Clinic or elsewhere, and a number for 1 of the laboratory directors in case the referring physician has additional questions. Increased urinary xanthine and hypoxanthine with low urinary uric acid are characteristic of xanthine oxidase deficiency. Increased urinary excretion of xanthine, hypoxanthine, and uric acid are indicative of hyperuricemia disorders treated with allopurinol.

**Reference Values:**
- HYPOXANTHINE 20-100 mcmol/24 hours
- XANTHINE 20-60 mcmol/24 hours


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**XX/XY in Opposite Sex Bone Marrow Transplantation, FISH**

**Clinical Information:** Bone marrow transplantation (BMT) continues to be an important treatment for patients with malignant hematologic disorders and bone marrow failure syndromes. Conventional cytogenetic studies can be performed to evaluate a mixture of donor and recipient cells in opposite sex bone marrow transplants at a sensitivity of approximately 5%. Interphase FISH testing for X and Y chromosomes in opposite sex bone marrow transplant specimens results in an improved sensitivity of approximately 0.5%.

**Useful For:** Evaluating engraftment success by determining the proportion of donor and recipient interphase cells present in opposite sex bone marrow transplant recipients Monitoring the proportion of host and recipient cells over time may be useful to identify significant clinical changes

**Interpretation:** Residual XX host cells are present in female BMT recipients when the percent of XX interphase cells exceeds the cutoff (>0.6%XX). Residual XY host cells are present in male BMT recipients when the percent of XY interphase cells exceeds the cutoff (>0.3%XY).

**Reference Values:**

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**BMTF 35259**
An interpretive report will be provided.

**Clinical References:** Dewald GW, Schad CR, Christensen ER, et al: Fluorescence in situ hybridization with X and Y chromosome probes for cytogenetic studies on bone marrow cells after opposite sex transplantation. Bone Marrow Transplant 1993;12:149-154

**Xylose Absorption Test (Adult 25g dose)**

**Clinical Information:** Several drugs can interfere with test results - Aspirin - Atropine - Cochine - Digitalis - Indomethacin - MAO inhibitors - Nalidixic acid - Neomycin - Opium alkaloids - Phenelzine

**Reference Values:**
Serum fasting specimen: No reference intervals for the fasting serum: it is used as a blank when testing the two-hour specimen.

Serum xylose at 2 hours:
17 years and older: 32-58 mg/dL

Xylose excretion, % dose 5 hr:
17-64 years: 16-40 %
65 years and older: 14-40 %

Xylose excretion, g/5 hr:
17-64 years: 4.0-10.0 g/5hrs
65 years and older: 3.5-10.0 g/5hrs

**Y Chromosome Microdeletions, Molecular Detection**

**Clinical Information:** Yq microdeletions involving some or all of the azoospermic factor (AZF) region are the most frequently identified cause of spermatogenic failure in chromosomally normal men with nonobstructive azoospermia (3%-15%) or severe oligospermia (6%-10%). Among unselected infertile males, the overall frequency of Yq microdeletions is approximately 3%. The relative frequency of Yq microdeletions makes the evaluation for them an important aspect of the diagnostic work up in infertile males, especially those with azoosperma or severe oligospermia. Most cases of Yq microdeletions occur de novo, and due to the consequential infertile phenotype, they are typically not transmitted. However, in cases where assisted reproductive technology (example: testicular sperm extraction followed by intracytoplasmic sperm injection) is used to achieve viable pregnancy, all male offspring born to a microdeletion carrier will carry the deletion and may be infertile. Men testing positive for 1 or more microdeletions who are enrolled in an in vitro fertilization treatment program may wish to consider alternative options to intracytoplasmic sperm injection (eg, donor sperm) and consultation with an experienced reproductive endocrinologist and medical geneticist is recommended. Most Y microdeletions are the result of homologous recombination between repeated sequence blocks. Testing for deletions involves investigating for the presence or absence of markers located within nonpolymorphic regions of the AZF region.

**Useful For:** Evaluating men with azoospermia, severe oligozoospermia, or otherwise unexplained male factor infertility

**Interpretation:** An interpretive report will be provided.

**Yeast Ident Panel C**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**Yellow Faced Hornet Venom, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>


**Yellow Jacket Venom, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
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<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**FYERS** 57374  
**Yersinia enterocolitica Antibodies, IgA, IgG and IgM by Immunoblot**

**Reference Values:**

- Yersinia enterocolitica, IgA by Immunoblot: Negative
- Yersinia enterocolitica, IgG by Immunoblot: Negative
- Yersinia enterocolitica, IgM by Immunoblot: Negative

**FYABS** 57847  
**Yo Antibody Screen with Reflex to Titer and Western Blot**

**Reference Values:**

- Yo Ab, IFA: Negative

Purkinje cells cytoplasmic antibody (Yo) can be found in approximately 50% of patients with paraneoplastic cerebellar degeneration (PCD). The presence of Yo antibody strongly suggests underlying gynecological cancer primarily of ovarian or breast origin. A negative assay for Yo antibody does not exclude the possibility of a malignant tumor.
**FYOG**

**57915**

**Yogurt (Lactobacillus bulgaricus) IgE**

**Interpretation:**

<table>
<thead>
<tr>
<th>Class IgE (kU/L)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35 Below Detection</td>
</tr>
<tr>
<td>0.35 – 0.69</td>
<td>Low Positive</td>
</tr>
<tr>
<td>0.70 – 3.49</td>
<td>Moderate Positive</td>
</tr>
<tr>
<td>3.50 – 17.49</td>
<td>Positive</td>
</tr>
<tr>
<td>17.50 – 49.99</td>
<td>Strong Positive</td>
</tr>
<tr>
<td>50.00 – 99.99</td>
<td>Very Strong Positive</td>
</tr>
<tr>
<td>&gt;99.99</td>
<td>Very Strong Positive</td>
</tr>
</tbody>
</table>

**Reference Values:**

<0.35 kU/L

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**ZAP70**

**83727**

**ZAP-70, Chronic Lymphocytic Leukemia (CLL) Prognosis**

**Clinical Information:**

B-cell chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. Its clinical course is highly variable with survival times ranging from months to decades. The standard procedure for estimating prognosis is clinical staging systems developed by Rai and Binet. In these staging systems, most CLL patients have early-stage disease. Genetic prognostic markers such as immunoglobulin heavy chain gene mutational status and FISH studies for specific chromosomal abnormalities have now been developed to refine the risk of progressive disease. CD38 and ZAP-70 have been identified as surrogate markers for mutation status and can be evaluated by flow cytometric immunophenotyping. ZAP-70 (70-kDa zeta-associated protein) is an intracellular tyrosine kinase discovered initially because of its role in T-cell signaling. It has also been found to be associated with the B-cell receptor in CLL. The expression of ZAP-70 (> or =20% of B cells) has been associated with an increased risk for an adverse outcome in B-cell CLL and is considered an important risk factor in these patients. ZAP-70 expression, if present, is constant throughout the patient's clinical course and thus is a valid risk marker regardless of when it is evaluated.

**Useful For:**

Assessing a risk factor for disease progression in patients with B-cell chronic lymphocytic leukemia

**Interpretation:** ZAP-70 expression is considered to be a risk factor for disease progression in patients with B-cell chronic lymphocytic leukemia (CLL). The threshold for ZAP-70 staining is established by using normal B cells as the negative cutoff value and comparing with background positive T-cell staining. -ZAP-70-negative (<20% of monoclonal B cells) CLL patients have a median time to treatment of 9.2 years. -ZAP-70-positive (> or =20% of monoclonal B cells) CLL patients have a median time to treatment of 2.9 years. See ZAP-70 Expression and Overall Survival Among Patients with B-Cell CLL in Multimedia for survival curves.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


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**NEZPP**

**89375**

**Zinc Protoporphyrin, Blood**

Current as of July 8, 2016 11:28 am CDT

800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Clinical Information:** The porphyrins are intermediaries in the heme synthesis pathway. When iron is not available for heme synthesis (e.g., iron deficiency), zinc protoporphyrin (ZPP) accumulates within RBCs. Lead inhibits several enzymes in the heme synthesis pathway and causes increased levels of RBC ZPP. ZPP is a biological marker of lead toxicity and was previously used, in conjunction with blood lead assays, to screen for lead poisoning in children. However, because of poor sensitivity and specificity, ZPP is no longer recommended for lead screening in children. However, ZPP remains a useful tool for monitoring treatment of individuals with confirmed elevated lead levels.

**Useful For:** Evaluating iron deficiency Monitoring treatment and environmental intervention of chronic lead poisoning

**Interpretation:** An elevated zinc protoporphyrin (ZPP) indicates impairment of the heme biosynthetic pathway. Elevated ZPP levels in adults may indicate long-term (chronic) lead exposure or may be indicative of iron deficiency anemia or anemia of chronic disease.

**Reference Values:**
<70 mcmol ZPP/mol heme

**Clinical References:**

**Zinc, 24 Hour, Urine**

**Clinical Information:** Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc also is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking mega-vitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Identifying the cause of abnormal serum zinc concentrations

**Interpretation:** Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 300 mcg/specimen to 600 mcg/specimen. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

**Reference Values:**
300-600 mcg/specimen
Reference values apply to all ages.
**Clinical Information:**

Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc also is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking mega-vitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Identifying the cause of abnormal serum zinc concentrations

**Interpretation:**

Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 300 to 600 mcg/L. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

**Reference Values:**

300-600 mcg/L

Reference values apply to all ages.

**Clinical References:**

physiologically important proteins. The peptidases, kinases, and phosphorylases are most sensitive to zinc depletion. Zinc is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet (excess copper or iron interfere with absorption) or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to phytate (fiber) and not available for absorption. Excess copper and iron in the diet (eg, iron supplements) interfere with zinc uptake. Once absorbed, the most common route of loss is via exudates from open wounds or gastrointestinal loss. Zinc depletion occurs in burn patients who lose zinc in the exudates from their burn sites. Hepatic cirrhosis causes excess loss of zinc by enhancing renal excretion. Other diseases that cause low serum zinc are ulcerative colitis, Crohn's disease, regional enteritis, sprue, intestinal bypass, neoplastic disease, and increased catabolism induced by anabolic steroids. The conditions of anorexia and starvation also result in low zinc levels. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Detecting zinc deficiency

**Interpretation:** Normal serum zinc is 0.66 to 1.10 mcg/mL. Burn patients with acrodermatitis may have zinc as low as 0.4 mcg/mL; these patients respond quickly to zinc supplementation. Elevated serum zinc is of minimal clinical interest.

**Reference Values:**
- 0-10 years: 0.60-1.20 mcg/mL
- > or =11 years: 0.66-1.10 mcg/mL

**Clinical References:**

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**Zinc/Creatinine Ratio, Random, Urine**

**Clinical Information:** Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc also is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking mega-vitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Identifying the cause of abnormal serum zinc concentrations

**Interpretation:** Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 300 to 600 mcg/g creatinine. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.
Reference Values:
300-600 mcg/g Creatinine
Reference values apply to all ages.


Ziprasidone (Geodone, Zeldox)
Reference Values:
Units: ng/mL
Expected plasma concentrations in patients taking Recommended Daily Dosages: Up to 220 ng/mL

Zolpidem (Ambien), serum or plasma
Reference Values:
Units: ng/mL
Expected hypnotic zolpidem concentrations in patients taking recommended daily dosages: up to 250 ng/mL.
Toxic range has not been established.

Zonisamide, Serum
Clinical Information: Zonisamide (Zonegran) is approved as adjunctive therapy for partial seizures refractory to therapy with traditional anticonvulsants. Zonisamide is the pharmacologically active agent; metabolites are not active. Essentially 100% of the zonisamide dose is absorbed. Zonisamide binds to erythrocytes; approximately 88% of circulating zonisamide is bound in erythrocytes. Because the erythrocyte-bound zonisamide is inactive, and binding varies with blood concentration, the relationship between serum level and dose is not linear. Time to peak zonisamide concentration is 2 to 4 hours; time to peak is delayed by co-administration with food to 4 to 6 hours. Zonisamide is metabolized by N-acetyl transferase (NAT1), cytochrome P4503A4 (CyP3A4), and uridine diphosphate glucuronidation (UDPG). Zonisamide is eliminated in the urine predominantly as the parent drug (35%), N-acetyl zonisamide (15%), and as the glucuronide ester of reduced zonisamide (50%). Co-administration of drugs that affect NAT1, CyP3A4, and UDPG activity, such as phenytoin and carbamazepine, will decrease zonisamide concentration. A typical zonisamide dose administered to an adult is 400 to 600 mg/day, administered in 2 divided doses. The apparent volume of distribution of zonisamide is 1.5 L/kg. Approximately 40% of the zonisamide circulating in the serum is bound to proteins. Zonisamide protein binding is unaffected by other common anticonvulsant drugs. The elimination half-life from plasma is 50 to 60 hours; the elimination half-life from erythrocytes is >100 hours. Since zonisamide is cleared predominantly by the kidney, the daily dosage of zonisamide given to patients with creatinine clearance <20 mL/min should be reduced. (1,2) Serum level monitoring is recommended for all patients to ensure appropriate dosing because: 1) patient response correlates with serum level, 2) serum level does not correlate with dose because of concentration-dependent erythrocyte binding, 3) elimination is affected by co-administration of drugs that affect NAT1, CyP3A4, and UDPG, and 4) renal function affects elimination. The most common toxicity associated with excessive serum level is drowsiness. Adverse effects not related to serum level include rash, increased serum creatinine and alkaline phosphatase, kidney stone formation, and bruising.
**Useful For:** Monitoring zonisamide therapy; recommended for all patients to ensure appropriate dosing

**Assessing compliance**

**Interpretation:** Steady-state zonisamide concentration in a trough specimen drawn just before next dose correlates with patient response, but not with dose. Optimal response to zonisamide occurs when trough zonisamide concentration is in the range of 10 to 40 mcg/mL. Peak serum concentration for zonisamide occurs 2 to 6 hours after dose, and time to peak is affected by food intake. Because carbamazepine activates glucuronidation, patients taking carbamazepine concomitantly with zonisamide have significantly lower zonisamide concentrations compared to patients on the same dose not receiving carbamazepine.

**Reference Values:**

10-40 mcg/mL

**Clinical References:**


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**Zucchini (Cucurbita spp) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**Zygosity Testing (Multiple Births)**

**Clinical Information:** Approximately 30% of twins are monozygotic (identical), while 70% are dizygotic (nonidentical or fraternal). Monozygotic twins originate from a single egg, and by definition have identical DNA markers throughout their genomes. Dizygotic twins, on the other hand, inherit their genetic complement independently from each parent and are no more likely to have genetic material in common than are any other full siblings. To date, literally thousands of polymorphic DNA markers have been identified. DNA markers are regions of DNA that display normal variability in the type or the number of nucleotide bases at a given location. One particular class of repetitive DNA that exhibits marked variability is microsatellites. With the use of such markers, it is possible to distinguish one individual from another because of differences detected at these polymorphic loci. Utilizing PCR followed by gel electrophoresis, the genotypes of a set of twins (triplets, etc.) are derived from the analysis of multiple markers. This genotype is compared to those of their parents to determine if the children are mono- or dizygotic. Any differences detected between siblings’ microsatellite markers indicate dizygosity. Many disorders are known to occur on a genetic basis though the genes have not been identified for all of them. If 1 member of a set of twins is diagnosed with a genetic disorder, determination of zygosity, in addition to other testing, may provide additional information regarding risk assessment of unaffected individuals. In addition, zygosity can be useful when evaluating for twin-twin transfusion syndrome during pregnancy or as part of a preorgan transplant workup for situations where one twin is donating an organ to another twin.

**Useful For:** Determining genetic risk for an individual whose twin or triplet is affected with a genetic disorder.
disorder for which a specific genetic test is not available (or such testing is uninformative) Assessment of risks prenatally when 1 fetus of multiples is known to be affected by a specific disorder Organ or bone marrow transplantation compatibility testing Familial or parental interest

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**