XomeDx: Frequently Asked Questions

1. **When is XomeDx, GeneDx’s whole exome sequencing (WES) test, useful?**
   Whole exome sequencing (WES) targets the protein-coding regions (exons) of the approximately 20,000 genes in the genome (the exome). It is a powerful diagnostic tool, providing a definitive diagnosis in 20-50% of patients (Yang, et al. N Engl J Med. 2013 Oct 17;369(16):1502-11, and GeneDx, Retterer et al., Genet Med. 2015 Dec 3).
   WES can be used to identify the molecular basis of a genetic disorder in individuals:
   - With a genetically heterogeneous disease as pathogenic findings could be present in many different genes
   - With a long list of differential diagnoses
   - With an atypical presentation of a genetic disorder
   - Who have exhausted other currently available genetic testing options

2. **What are the different WES tests that GeneDx offers and how do they differ?**
   GeneDx offers multiple whole exome sequencing tests: XomeDx, XomeDxXpress, XomeDxPlus and XomeDxSlice. For more information please visit [www.genedx.com/xomedx](http://www.genedx.com/xomedx).
   - **XomeDx** is whole exome sequencing (protein-coding nuclear genes only) with a phenotype-targeted report. Unless the patient opts-out in writing, we will also report pathogenic and expected pathogenic variants we find in genes recommended in the American College of Medical Genetics and Genomics (ACMG) policy statement, regarding the reporting of secondary findings in clinical exome sequencing for the XomeDx, XomeDxPlus, and XomeDxXpress tests (Green, et al. Genet Med 2013:15(7):565-574).
   - **XomeDxXpress** is the XomeDx test with an expedited turn-around-time providing verbal results within 7 days, and a written report within 2 weeks.
   - **XomeDxPlus** is a combined test including whole exome sequencing, in addition to sequencing and deletion testing of the mitochondrial genome.
   - **XomeDxSlice** captures and sequences the whole exome, but analysis is targeted to a limited and specific phenotype-driven gene list. A list of genes to be analyzed is determined prior to testing by the ordering provider in consultation with GeneDx where indicated. To review gene coverage and submit an XomeDxSlice gene list, please visit the SliceTool on our website: [www.genedx.com/xomedx-slice-tool/](http://www.genedx.com/xomedx-slice-tool/).

3. **What does GeneDx need to perform XomeDx testing?**
   - Proband’s specimen (blood, DNA, dried blood spot, or oral rinse)
   - Requisition form signed by the ordering provider and consent form signed by the patient
   - Medical records, including prior test results, consult notes, pedigree, etc.
   - Specimens from additional family members if available, and accompanying consent forms

4. **What is the cost of XomeDx?**
   GeneDx can bill all commercial insurance, and the patient is responsible for only the co-pay, co-insurance and unmet deductible as dictated by his or her insurance carrier. GeneDx will perform a benefit investigation and attempt to contact the patient if the patient’s out-of-pocket cost is expected to be greater than $100. If GeneDx is unsuccessful in their attempts to contact the patient, it will be the patient’s responsibility to contact GeneDx to determine the out-of-pocket cost. GeneDx will work with the patient if the patient has financial difficulty and will offer a financial assistance program to those who qualify. Additional information can be found on our billing page ([www.genedx.com/xomedxbilling](http://www.genedx.com/xomedxbilling)).
5. What is the turn-around-time for the XomeDx test?

Please visit our XomeDx test information page for the turn-around-time for this test: www.genedx.com/xomedx. Results are sent directly to the ordering provider.

6. Whose specimens should be sent for XomeDx and what testing is performed?

When a trio is sent for XomeDx, XomeDxXpress and XomeDxPlus, whole exome sequencing is always performed on each member of the trio. This improves the sensitivity of the analysis when compared to testing only the proband (affected individual in the family). Biological parents are typically the most informative samples and are accepted whenever possible. In some cases, siblings of the proband will be requested. Sometimes testing distantly related family members can be helpful. GeneDx will decide, in consultation with the ordering provider, the individuals who can optimize our ability to identify a genetic cause of the patient’s phenotype. We will also discuss the type of testing that is most useful and cost-effective (i.e. whole exome sequencing or targeted testing of variants to determine segregation). All individuals’ samples should be submitted at the beginning of testing. If additional relatives are indicated to be arriving separately from the proband, testing may be held for a short period of time until all samples are received. In general, only a single report will be issued for the proband. However, the report will describe the inheritance and segregation of reported variants for all individuals tested.

7. What if extended family members want to be tested for a variant identified in a patient by XomeDx testing?

Family members can be tested for the variants identified in the proband for a fee. Please refer to the information in the carrier testing page for details (www.genedx.com/carriertesting).

8. Can you use WES to screen the parents for carrier status of recessive diseases?

No, a test designed for universal carrier screening (such as Inherigen by GenPath Women’s Health www.genpathdiagnostics.com/womens-health/inherigen) is a better way to obtain this information. In addition, strict carrier status will not be reported for a proband unless it is possible that the finding may be related to the reported phenotype in that individual. This follows the American Academy of Pediatrics (AAP) guidelines recommending carrier testing not be performed on children.

9. How does GeneDx identify variants that are associated with the patient’s phenotype?

WES identifies hundreds of thousands of variants. Variants are filtered using a variety of factors including population frequency, presence of gene and/or variant in the Human Gene Mutation Database (HGMD) or other databases, inheritance pattern, phenotype, severity of sequence change, and function in biological pathways.

10. Are there any findings that will NOT be reported?

A single report will be issued on the proband. No report will be issued on the parents or other relatives. Variations known to be benign (not associated with disease) and/or commonly seen in many other healthy individuals will not be reported. If a patient opts-out of receiving secondary findings, we will not analyze or report variants in the ACMG recommended genes unless they are related to the patient’s phenotype.

11. Will the analysis identify any genetic information that is unrelated to the patient’s reported phenotype?

Due to the fact that many different genes and conditions are being analyzed by the XomeDx test, this test may reveal incidental findings, and the individual may learn genetic information about themselves or their family that is not directly related to the reason for ordering the test. Incidental findings are variants identified by the XomeDx test in genes that are unrelated to the individual’s clinical features reported to GeneDx at the time of testing, but are often medically actionable findings. They are different from variants in the list of genes included for secondary findings recommended by ACMG, which represent genes that are actively reviewed as part of WES (unless the patient requests to opt-out of receiving ACMG secondary findings).
12. Does WES detect copy number variants?
WES may detect copy number variants (deletions and duplications that are 50bp or larger). As with other types of variants, any copy number variant that is included in a GeneDx report has been confirmed via an alternate test method. The sensitivity of WES to identify CNVs compared with other methods in a diagnostic setting is not currently known.

13. Is it possible to reflex to XomeDx if XomeDxSlice is negative?
Yes, you will need to submit a completed add-on form for “Reflex to XomeDx”, a completed consent document, and submit additional family member samples if possible. For billing information regarding reflex testing to XomeDx if XomeDxSlice is negative, please contact the GeneDx Billing department at 301-519-2100.

14. Will GeneDx offer reanalysis of WES data, and what is the cost?
The ordering provider may request a reanalysis of the exome sequencing data for XomeDx, XomeDxXpress, and XomeDxPlus up to one year after the test report was issued. The first reanalysis can be requested at no charge. GeneDx may also contact the ordering provider and recommend a reanalysis if our internal data mining reveals a new reportable variant. Although reanalysis has a much higher yield when initiated by the laboratory than by the provider, a provider-initiated reanalysis is more worthwhile when there is new clinical information that is provided for the patient’s reanalysis.

15. What platform is GeneDx using?
Whole exome sequencing is performed with GeneDx’s proprietary method that combines Agilent Clinical Research Exome target enrichment and KAPA Biosystems library preparation kits. We are using the Illumina HiSeq 2500 and 4000 sequencing systems for next-generation sequencing.

16. What are the statistics for coverage/quality?
On average, we are able to evaluate 96% of an exome at a minimum of 10x coverage, with approximately 99% coverage for over 4,500 disease-associated genes. Certain genes may have low coverage because no probes are available, or the gene falls within a region not amenable to sequencing. We will provide specific information in the report about how much of the exome was evaluated for a particular patient.

17. Can we have access to the aligned sequence data?
The sequence data generated by the XomeDx test can be requested by the ordering health care provider. Please see the Consent for Release of Exome Data form and FAQs document on the Special Services tab at www.genedx.com/xomedx.