Cigna Medical Coverage Policy

Subject: Genetic Testing for Tay-Sachs Disease

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- Genetic Disease Screening Panels
- Genetic Testing of Heritable Disorders
- Preimplantation Genetic Diagnosis
- Stem-Cell Transplantation for Inherited Metabolic Disorders

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies including plans formerly administered by Great-West Healthcare, which is now a part of Cigna. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supercedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2012 Cigna

Coverage Policy

Cigna covers genetic testing for Tay-Sachs disease (TSD) and variants (e.g., Sandhoff disease) as medically necessary when ANY ONE of the following medical necessity criteria is met:

- For confirmatory (i.e., diagnostic) testing in EITHER of the following situations:
  - A symptomatic individual has clinical features suggestive of TSD or variants and abnormal HEX A or HEX B enzymatic testing, but conventional studies have been completed for this individual and a definitive diagnosis remains uncertain.
  - An asymptomatic individual with abnormal HEX A or HEX B enzymatic testing in order to evaluate for the presence of a pseudodeficiency allele.

- For predictive testing when there is an affected family member (first-or second-degree relative*) who has confirmed TSD or a variant (e.g., Sandhoff disease)

- For prenatal or preconception carrier testing when the individual is the reproductive partner of an individual with chronic or adult onset HEX A or HEX B deficiency and the couple has the capacity and intention to reproduce

- For prenatal testing of a fetus or preimplantation genetic diagnosis (PGD) in ANY of the following situations:
Both parents are heterozygous, and molecular genetic testing has ruled out pseudodeficiency allele in either parent.

One parent is known to be heterozygous, and the other parent has inconclusive enzymatic activity.

The mother is known to be heterozygous, and the father’s status is unknown and is unavailable for testing.

One parent has chronic or adult-onset HEX A or HEX B deficiency

* A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

* A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

Cigna does not cover genetic testing for the susceptibility to TSD in the general population, because such screening is considered not medically necessary or of unproven benefit.

General Background

Tay-Sachs disease (TSD) and Sandhoff disease, considered by some to be a variant of TSD, are autosomal recessive neurodegenerative disorders caused by gene mutations. These mutations are very rare in the general population. Although occurring in all ethnic and racial groups, the mutations causing TSD are more common among individuals of Ashkenazi (eastern and central European) Jewish heritage, and certain individuals of French-Canadian and Cajun descent with a disease incidence of 1/3,000 and a carrier frequency of 1/30 (American College of Obstetrics and Gynecologists [ACOG], 2009 (National Institutes of Health [NIH], 2008a,b). Sandhoff disease occurs more commonly in the non-Jewish population (Johnston, 2007).

These diseases are classified as GM2 ganglioside disorders, also known as lysosomal storage disorders. Each results from a deficiency in beta-hexosaminidase enzyme activity and the lysosomal accumulation of fatty acid GM2 gangliosides (McGovern, 2007). Tay-Sachs disease (TSD) is caused by a mutation of an alpha subunit of the hexosaminidase A (HEXA) gene chromosomal locus 15q23-q24, which encodes the alpha subunit of the beta-hexosaminidase enzyme. This is the only gene associated with HEXA deficiency. The HEXB gene chromosomal locus 5q13, encodes the beta subunit of the beta-hexosaminidase enzyme. In Sandhoff disease, mutations in the gene coding for the beta subunits of HEXA and hexosaminidase B (HEXB) occur on chromosome 5.

TSD and Sandhoff disease are clinically indistinguishable (NIH, 2009). Each disease is classified into three phenotypes: acute infantile, which is rapidly progressive and results in death before age four; subacute, or juvenile, which has a later onset and survival in late childhood or adolescence; and chronic or late-onset, characterized by longer-term survival and variable neurological symptoms. The most common and severe form is classic infantile, resulting from an absence of, or little beta-hexosaminidase enzyme function.

To date, there is no cure or effective treatment. The use of enzyme replacement therapy has been explored; however, this has not been shown to be effective. Clinical trials testing the potential of a substrate reduction drug are in progress. At present, treatment is primarily supportive and directed to provide adequate nutrition, hydration, management of infectious disease, and control of seizures.

Testing Strategy

The outcome for TSD is usually death before the age of four years and current therapeutic attempts to improve the survival rate have been unsuccessful. It is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented (Johnston, 2007). Deoxyribonucleic acid (DNA) testing to confirm a diagnosis and prenatal or preconception carrier screening allow for the opportunity for reproductive choice, and for supportive medical treatment planning, as well as the opportunity for
preparation of the family for a child with this disorder. Prenatal testing of a fetus and preimplantation genetic diagnosis (PGD) also allow for the opportunity for reproductive choice. PGD allows embryos created in-vitro to be tested before implantation.

Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained genetics professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional who is unaffiliated with the genetic testing lab performing the test(s).

Confirmatory/Diagnostic Testing: An assay of enzymatic activity in serum or leukocytes using synthetic substrates provides a simple, inexpensive, and highly accurate method for heterozygote identification. Data from large scale proficiency testing suggest that analytic sensitivity is about 98%, with estimates of clinical sensitivity of 95%, and an estimate of negative predictive value of 1.1% (Monaghan, 2008).

Serum is used for testing males and for testing women who are not pregnant and who are not using oral contraceptives. Leukocytes are used for testing women who are pregnant, for women who are using oral contraceptives, and for any individual who has a tissue destructive disorder (e.g., diabetes mellitus, hepatitis, rheumatoid arthritis) or who is taking unusual medications and whose serum HEXA enzymatic activity is in an inconclusive range (Kaback, 2004).

When enzymatic testing is abnormal, DNA analysis of these genes can be performed in a symptomatic individual in order to identify mutations or the presence of a pseudodeficiency allele. In an asymptomatic individual with abnormal HEXA or HEXB enzymatic testing, genetic testing can be used to evaluate for the presence of a pseudodeficiency allele.

Prenatal or Preconception Carrier Testing: An enzymatic measurement of HEXA activity in serum, white blood cells, or fetal trophoblastic cells can distinguish carriers of TSD from noncarriers. Deoxyribonucleic acid (DNA)-based carrier testing may be necessary to clarify an ambiguous enzyme test and confirm a variant form of the disease.

A limitation of deoxyribonucleic acid (DNA)-based carrier testing is that not all known mutations in the HEXA or HEXB genes are detected by the test. At this time at least 120 mutations of the HEXA gene and >20 mutations of the HEXB genes are known; others have yet to be identified. The tests currently available detect about 95% of carriers of Ashkenazi Jewish background and about 60% of non-Jewish individuals; some who are carriers will not be identified by DNA analysis alone.

Both HEXA and HEXB enzymatic and HEXA and HEXB DNA mutation analysis can be used to identify carriers among at-risk family members. Identification of the specific HEXA or HEXB mutations by DNA testing of the carrier parents or proband is appropriate for purposes of prenatal testing and for identification of carriers among other family members. It is also appropriate to offer carrier detection to the partners of individuals with chronic or adult-onset HEXA or HEXB deficiency.

Prenatal Testing of a Fetus or Preimplantation Genetic Diagnosis (PGD): Parental mutations must be known for PGD, whereas enzyme testing is possible on a prenatal sample. Not all indications for prenatal testing of a fetus apply to PGD. In certain situations prenatal testing may be appropriate to aid in reproductive planning. Indications include when HEXA or HEXB enzyme testing has shown both parents to be heterogeneous and molecular genetic testing has ruled out the presence of a pseudodeficiency allele, when one parent is a known heterozygote and the other parent has inconclusive enzymatic activity and no disease-causing mutation has been found on DNA analysis, and when the mother is a known heterozygote and the father is unknown or unavailable for testing. When the disease-causing mutations have been identified in both parents, prenatal testing can be performed by mutation analysis of the HEXA or HEXB genes in fetal DNA extracted from cells obtained by either chorionic villi sampling (CVS) or amniocentesis.

Professional Societies/Organizations
American College of Obstetricians and Gynecologists (ACOG): ACOG published a Committee Opinion paper regarding carrier screening for Tay-Sachs disease (TSD) (Statement Number 318 (October 2005)
Tay-Sachs and variant diseases (e.g., Sandhoff) are progressive neurodegenerative autosomal recessive disorders which are ultimately fatal. Enzymatic testing and DNA mutation analysis can be used to identify affected persons or carriers, and is appropriate for purposes of supportive medical treatment planning and for reproductive planning.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

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<th>CPT® Codes</th>
<th>Description</th>
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<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S) (code effective 0/01/2012)</td>
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<td>Code</td>
<td>Molecular Pathology Procedure Details</td>
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<td>83080</td>
<td>b-Hexosaminidase, each assay</td>
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<td>83890</td>
<td>Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)</td>
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<td>83891</td>
<td>Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie., DNA or RNA)</td>
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<td>83892</td>
<td>Molecular diagnostics; enzymatic digestion, each enzyme treatment</td>
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<tr>
<td>83894</td>
<td>Molecular diagnostics; separation by gel electrophoresis (e.g., agarose, polyacrylamide), each nucleic acid preparation</td>
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<td>83898</td>
<td>Molecular diagnostics; amplification, target, each nucleic acid sequence</td>
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<td>83900</td>
<td>Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences</td>
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<td>Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)</td>
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<td>Molecular diagnostics; mutation identification by sequencing, single segment, each segment</td>
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<td>83905</td>
<td>Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment</td>
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<td>Molecular diagnostics; interpretation and report</td>
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**HCPCS Codes Description**

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**ICD-9-CM Diagnosis Codes**

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<td>330.1</td>
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References

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disease


## Policy History

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<tr>
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<td>Cigna HealthCare</td>
<td>3/15/2008</td>
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