



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for Tay-Sachs Disease

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

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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 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 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 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 (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). TSD is caused by a mutation of an alpha subunit of the hexosaminidase A (HEX A) gene on chromosome 15; in Sandhoff disease, mutations in the gene coding for the beta subunits of HEX A and hexosaminidase B (HEX B) occur on chromosome 5.

TSD and Sandhoff disease are clinically indistinguishable (NIH, 2009a). 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.

Clinical Diagnosis

The HEX A gene chromosomal locus 15q23-q24, which encodes the alpha subunit of the beta-hexosaminidase enzyme, is the only gene associated with HEX A deficiency. The HEX B gene chromosomal locus 5q13, encodes the beta subunit of the beta-hexosaminidase enzyme.

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 HEX A enzymatic activity is in an inconclusive range (Kaback, 2004).

Testing Strategy

The outcome for Tay-Sachs disease (TSD) is usually fatal and current therapeutic attempts 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). Carrier screening and diagnostic testing allows 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 and preimplantation genetic diagnosis allows for the opportunity for reproductive choice. PGD allows embryos created in-vitro to be tested before implantation.

Confirmatory/Diagnostic: When enzymatic testing is abnormal DNA analysis of these genes can be performed in symptomatic individuals in order to identify the mutations and in asymptomatic individuals to evaluate for the presence of a pseudodeficiency allele.

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

A limitation of DNA-based carrier testing is that not all known mutations in the HEX A or HEX B genes are detected by the test. At this time at least 120 mutations of the HEX A gene and >20 mutations of the HEX B 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 HEX A and HEX B enzymatic and HEX A and HEX B DNA mutation analysis can be used to identify carriers among at-risk family members. Identification of the specific HEX A or HEX B 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 HEX A or HEX B deficiency.

Prenatal Testing: Prenatal testing can be performed when the following conditions exist:

- A HEX A or HEX B enzyme assay has shown both parents to be heterozygous, and molecular genetic testing has ruled out the presence of a pseudodeficiency allele in either parent.
- If the disease-causing mutations have been identified in both parents, prenatal testing can be performed by mutation analysis of the HEX A or HEX B genes in fetal DNA extracted from cells obtained by either chorionic villi sampling (CVS) or amniocentesis.
- One parent is a known heterozygote; the other parent has inconclusive enzymatic activity; and no disease-causing mutation has been found on DNA analysis.
- The mother is a known heterozygote, and the father is unknown and/or unavailable for testing

Evidence to support population-based screening programs providing health benefits for the general population is lacking at this time (Hayes, 2003).

Professional Societies/Organizations

American College of Obstetricians and Gynecologists (ACOG): ACOG published a Committee opinion statements regarding carrier screening for Tay Sachs disease (Statement Number 318 (October 2005) (Replaces No. 162, November 1995) which notes: "Tay-Sachs disease (TSD) is a severe, progressive neurologic disease that causes death in early childhood. Carrier screening should be offered before pregnancy to individuals and couples at high risk, including those of Ashkenazi Jewish, French-Canadian, or Cajun descent and those with a family history consistent with TSD. If both partners are determined to be carriers of TSD, genetic counseling and prenatal diagnosis should be offered."

American College of Medical Genetics (ACMG): Regarding genetic testing for TSD, on behalf of the ACMG, Gross et al. (2008) recommended that the guidelines of the ACOG be followed.

Summary

Tay-Sachs and variant diseases (e.g., Sandhoff) are progressive neurodegenerative autosomal recessive disorders. 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:

CPT^{®*} Codes	Description
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (i.e., DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83894	Molecular diagnostics; separation by gel electrophoresis (e.g., agarose, polyacrylamide), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83912	Molecular diagnostics; interpretation and report

HCPCS Codes	Description
S3847	Genetic testing for Tay-Sachs disease

ICD-9-CM Diagnosis Codes	Description
330.1	Cerebral lipidoses

***Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	3/15/2008	0059	Genetic Testing for Tay-Sachs Disease

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