Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/25**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Tay-Sachs Disease

Description/Background

The GM2 gangliosidoses are a group of lysosomal lipid storage disorders which include Tay-Sachs disease (TSD). GM2 gangliosides are large lipid molecules that are found on surfaces of nerve cell membranes; they are continuously synthesized and degraded. Lysosomes are organelles within the cell that contain approximately 50 different enzymes that are involved in digestion of toxic substances and removal of waste. One such enzyme is beta-hexosaminidase A (β-hexosaminidase A, or Hex A), which is responsible for normal catabolism of the GM2 ganglioside substrate. When there is absence or deficiency of Hex A, the substrate accumulates in cells resulting in cell death, most notably cells in the brain and spinal cord. The *HEXA* gene provides instructions for making a subunit of Hex A, and variants in the *HEXA* gene result in underproduction of Hex A. The severity of TSD disease is directly related to the amount of Hex A that the body produces.

Tay-Sachs has been found to have several forms: infantile (or classic), juvenile and adult (or late-onset). Only one form of Tay-Sachs occurs in a family.

Infantile Tay-Sachs: The infantile form is characterized by almost complete lack of Hex A enzyme activity, and is the most severe form. Infants may appear unaffected at birth; however, symptoms appear in the first few months of life. Symptoms include loss of learned skills (regression), seizures, and loss of muscle and mental functions. A classic symptom is the finding of a cherry-red spot on the macula of the eye from exposure of the choroid. Children with this form do not survive past early childhood.

Juvenile Tay-Sachs: This form has a range of severity with symptoms appearing any time during childhood, but generally between ages 2 and 5. Symptoms include behavior problems, gradual loss of skills, frequent respiratory infections, and seizures. Children with this form typically do not survive past their teenage years.

Adult Tay-Sachs: This is the least severe form with symptoms appearing in late childhood to adulthood. Symptoms may include clumsiness, muscle weakness, psychiatric disorders, and gradual loss of skills, often leading to the need for mobility assistance. Intellect and behavior become impaired in some cases. The lifespan varies from shortened to unaffected.
Tay-Sachs is a rare, autosomal recessive neurodegenerative disease. It is estimated that the risk of being a Tay-Sachs carrier is 1 in 250-300 in the general population. There are several population groups that are at higher risk. Individuals of Ashkenazi (Eastern or Central European) Jewish descent have a 1 in 25-30 risk of being a carrier of the gene mutation. Additionally, individuals of Eastern Quebec French Canadian, Southern Louisiana Cajun or Old Order Amish Pennsylvania Dutch descent also have a risk of about 1 in 30 of being carriers. There is also evidence that individuals of Irish or British Isle descent have a risk of about 1 in 50.

Measurement of Hex A enzyme activity in serum, white blood cells, or fetal trophoblastic cells can be used as an initial screening test for TSD mutation carriers. However, in some cases the enzyme test may not be diagnostic, and DNA (deoxyribonucleic acid) analysis may be necessary.

DNA testing may also be indicated to confirm results of a positive enzyme test in individuals who are not in a high-risk population, where a condition known as pseudodeficiency may exist. In the laboratory enzyme assay, a synthetic substrate is used. If an individual has a pseudodeficiency allele, the enzyme's ability to convert the synthetic substrate is impaired, resulting in a false positive result. Enzymes encoded by pseudodeficiency alleles can process natural substrate normally, or at a level that does not result in disease.

Regulatory Status:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several commercial laboratories currently offer genetic testing for Tay-Sachs disease; they include testing of 5 pathological genes as well as 2 pseudodeficiency alleles.
Laboratory Corporation of America
Integrated Genetics (a division of LabCorp)
Mayo Medical Laboratories
ARUP Laboratories
Quest Diagnostics

Medical Policy Statement

Genetic testing for Tay-Sachs disease (*HEXA* gene) is considered established. Genetic testing is considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

For preimplantation testing, refer to the member's specific certificate for coverage of in-vitro services

Inclusions:
Genetic testing of *HEXA* gene (for Tay-Sachs disease) is established in individuals:

- who belong to high-risk populations (eg, Ashkenazi Jewish, French-Canadian, Louisiana Cajun, Pennsylvania Dutch or Irish / British Isle heritage)
- unsure of their Ashkenazi Jewish heritage
- with a blood relative with Tay-Sachs disease
- whose partners have been positively-identified as a carrier
- with ambiguous β-hexosaminidase A enzyme assay results
- with low β-hexosaminidase A enzyme levels, who are not in a high-risk population, where pseudodeficiency is suspected
- who are suspected of having Tay-Sachs disease based on symptoms:
  - for confirmation of diagnosis OR
  - for testing to provide information to relatives at risk

Preimplantation or prenatal genetic testing of *HEXA* gene (for Tay-Sachs disease) is established:

- when both parents are carriers of *HEXA* gene variants, OR
- in families with genetically confirmed TSD

Note: Genetic counseling should be offered prior to testing to explain the significance of anticipated test results.

Exclusions:
Genetic testing when used as screening for Tay-Sachs disease in the general population.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81255* 81406*

Other codes (investigational, not medically necessary, etc.):

N/A

*Not covered for Medicare

Rationale

RISK-BASED CARRIER SCREENING

The purpose of carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child and to inform reproductive decisions.

Risk-based carrier screening can be pan-ethnic (eg, cystic fibrosis [CF], spinal muscular atrophy) or based on disease and carrier risk determined by family history, ethnicity, and race. Pan-ethnic screening is recommended when carrier rates in the general population approach or exceed those judged to offer clinical utility and/or ethnicity may be difficult to evaluate. Risk-based carrier screening is performed by genotyping for a set of defined variants (in contrast to identifying variants by sequencing an entire gene).

Risk-based carrier screening involves testing for a defined set of pathogenic variants for specified conditions. The analytic validity is expected to be high in qualified laboratories. The clinical validity is sufficiently defined and reflected in estimated residual risk. There is sufficient evidence to support the clinical utility of risk-based screening.

The HEXA gene was isolated in 1985, found in the long arm of chromosome 15 at position 23. Since that time, more than 100 variants have been identified. Current tests can detect about 95% of carriers that are of Ashkenazi Jewish background; whereas only 60% of carriers in the general population can be identified.

The most frequent pathological variant found in those of Ashkenazi Jewish heritage is a homozygous insertion in exon 11, noted to be 1278insTATC. This variant is found in about 82% of those with TSD. The next most frequent variant is 1421+1G>C (also noted as IVS12, G-C, +1); followed by G269S, which is the most common variant found in late-onset Tay-Sachs. In those of French-Canadian heritage, the most common variant is a large deletion, noted to be 7.6-kb. Variants commonly found in non-Ashkenazi Jewish populations are 1278insTATC, G269S and 1073+1G>A. About 35% of non-Jewish individuals also carry 1 of 2 pseudodeficiency alleles[3,4].

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

ACOG Committee Opinion, March 2017 – Carrier Screening for Genetic Conditions
Tay-Sachs Disease[1] (reaffirmed 2023)

- Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease also should be offered screening.
- When one member of a couple is at high risk (ie, of Ashkenazi Jewish, French-Canadian, or Cajun descent or has a family history consistent with Tay-Sachs disease) but the other partner is not, the high-risk partner should be offered screening. If the high-risk partner is found to be a carrier, the other partner also should be offered screening.

- Enzyme testing in pregnant women and women taking oral contraceptives should be performed using leukocyte testing because serum testing is associated with an increased false-positive rate in these populations.
- If Tay–Sachs disease screening is performed as part of pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay–Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel.

American College of Medical Genetics and Genomics (ACMG) Practice Guideline: Carrier screening in individuals of Ashkenazi Jewish descent – 2008[2] **(retired)**

> "We recommend that carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease be offered to all Ashkenazi Jews who are pregnant or considering pregnancy, according to current American College of Medical Genetics and/or the American College of Obstetricians and Gynecologists (ACOG) guidelines."

National Tay-Sachs & Allied Diseases Association of Delaware Valley
NTSAD Position Statement "Standards for Tay-Sachs Carrier Screening" 2009[3,7]

> "As the American population continues to intermarry at a significant rate, leading to a more diverse genetic admixture, enzymatic analysis is recommended as the primary testing modality for identifying carriers for Tay-Sachs disease. DNA testing can and should be used to confirm Tay-Sachs enzyme results, to clarify indeterminate enzyme results, to identify cases of pseudodeficiency, as well as to provide molecular information for reproductive procedures and genetic counseling (Kaback, 1999)."

NTSAD Position Statement "Standards for Tay-Sachs Carrier Screening" – 2019 update[8]
Summary points

- Full-exon gene sequencing via NGS is a highly sensitive molecular test that detects coding sequence changes throughout the HEXA gene for Tay-Sachs disease and has a high carrier detection rate across all ethnic groups. In rare cases, this technology is limited by the inability to detect some non-coding pathogenic variants or to properly classify some VUS.
- Genotyping is a molecular test that detects the presence of a select number of pre-specified pathogenic variants within the HEXA gene. It is less sensitive than full-exon gene sequencing by NGS, and in most instances, should not be the test of choice when screening for carrier status for TSD.
- Tay-Sachs disease carrier screening via Hex A enzyme activity testing is a sensitive assay for carrier detection. Of note, subsequent molecular testing may be needed to allow for utilization of reproductive options for carrier couples, and leukocyte testing (rather than serum testing) should be ordered for Tay-Sachs disease carrier screening in women who are pregnant or using oral contraceptive medication.
- Current data supports a shift toward the routine use of full-exon HEXA NGS for Tay-Sachs carrier screening in individuals of all ethnic backgrounds due to the benefits and few limitations of NGS, while continuing to regard Hex A enzyme activity testing as another reliable method for Tay-Sachs carrier status detection.

Government Regulations

National:

There is no national coverage determination.

Local:

Wisconsin Physicians Service Insurance Corporation[11]
Local Coverage Article: Billing and Coding MolDx: HEXA Gene Analysis (A55168)
Original Effective Date: 02/16/2017
Revision Effective Date: 12/28/2023
Retired: 05/30/2024

Effective for dates of service on and after February 7, 2013.
The clinical diagnosis of Hexosaminidase A deficiency, a disorder also known as Tay-Sachs disease characterized by progressive weakness, loss of motor skills, and increased startle reflex in infants, relies on blood tests that result in absent or near absent beta-hexosaminidase A (HEX A) enzymatic activity. Molecular genetic testing identifies HEXA gene mutation carriers at risk for conceiving offspring with the disease. Therefore, HEXA genetic testing is not a Medicare benefit and is a statutorily excluded service. In addition to single gene testing, MolDX will also deny panels of tests that include the HEXA gene as a statutorily excluded service.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling
Genetic Testing for Bloom Syndrome
Genetic Testing – Carrier Screening for Genetic Diseases
Genetic Testing – Preimplantation
Invasive Prenatal (Fetal) Diagnostic Testing

References

1. American College of Obstetrics and Gynecology, Carrier Screening for Genetic Conditions. ACOG Committee Opinion No. 691, March 2017 reaffirmed 2023. (Replaces Committee Opinion Numbers 318 October 2005, 432 May 2009, 442 October 2009, 469 October 2010 and 486 April 2011.) Carrier Screening for Genetic Conditions | ACOG accessed 2/25/25
2. American College of Medical Genetics and Genomics (ACMG) Practice Guideline: Carrier screening in individuals of Ashkenazi Jewish descent – 2008 Retired Practice Guidelines (acmg.net) accessed 2/25/25
3. Kaback M. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. European Journal of Pediatrics. Vol. 159, Supplement No. 3, December 2000, pp. S192-S195.
4. Markel H. Appendix 6. Scientific Advances and Social Risks: Historical Perspectives of Genetic Screening Programs for Sickle Cell Disease, Tay-Sachs Disease, Neural Tube

Defects and Down Syndrome, 1970-1997. Final Report of the Task Force on Genetic Testing, 2007.
5. McDowell GA, et al. The presences of two different infantile Tay-Sachs mutations in a Cajun population. AM J Hum Genet. Nov 1992; 51(5): 1071-1077.
6. National Human Genome Research Institute. Learning About Tay-Sachs Disease. https://www.genome.gov/10001220/learning-about-taysachs-disease/ Accessed 2/25/25
7. National Tay-Sachs & Allied Diseases Association of Delaware Valley. http://www.tay-sachs.org/taysachs_disease.php Accessed 2/25/25
8. National Tay-Sachs & Allied Diseases Association of Delaware Valley. 2019 NTSAD Tay-Sachs Carrier Screening Position Statement. Microsoft Word - NTSAD-Position-Statement-TS-Carrier-Screening.2019.11.13.FINAL.docxAccessed 2/25/25
9. OMIM 272800 Tay-Sachs Disease https://www.omim.org/entry/272800 Accessed 2/25/25
10. OMIM 606869 Hexosaminidase A https://www.omim.org/entry/606869#genotypePhenotypeCorrelations Edited 4/6/2018. Accessed 2/25/25
11. Wisconsin Physicians Service Insurance Corporation, MAC – Part B 08202 – MAC B. Local Coverage Article: Billing and Coding MolDx: HEXA Gene Analysis (A55168) Original Effective Date: 02/16/2017, Revision Effective Date: 12/28/2023. Retired 05/30/24

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 2/25/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/09	3/12/09	2/10/09	JUMP policy established
1/1/12	10/11/11	11/9/11	Routine maintenance
5/1/12	2/21/12	2/21/12	Routine maintenance, CPT code 81255 added to policy
7/1/13	4/16/13	4/22/13	Routine maintenance. Added CPT code 81406
11/1/14	8/21/14	8/25/14	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance Updated local Medicare information
7/1/18	4/17/18	4/17/18	Routine maintenance. Description, MPS, inclusions, rationale updated.
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (jf) Vendor Managed: NA
7/1/24	4/16/24		Routine maintenance (jf) Vendor Managed: NA
7/1/25	4/15/25		Routine maintenance (jf) Vendor Managed: NA • Safety and effectiveness removed from MPS

Next Review Date: 2nd Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR TAY-SACHS DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria applies.
BCNA (Medicare Advantage)	See Government Regulations Section of policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.