

Overview

Useful For

Carrier detection and diagnosis of Tay-Sachs disease

Carrier detection and diagnosis of Sandhoff disease

Testing Algorithm

If result interpretation is consistent with carrier, indeterminate, or affected for Tay-Sachs disease or Sandhoff disease, then next-generation sequencing to detect single nucleotide and copy number variants for *HEXA* or *HEXB*, respectively, will be performed at an additional charge.

See [Tay-Sachs and Related Disorders Diagnostic Testing Algorithm](#)

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Biochemical Genetics Patient Information](#)
- [Tay-Sachs and Related Disorders Diagnostic Testing Algorithm](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CGPH	Custom Gene Panel, Hereditary	Yes	No
HEXBZ	HEXB Gene, Full Gene Analysis	Yes	No

Method Name

Heat Inactivation/Fluorometric/Semiautomated

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD

Ordering Guidance

The following tests are available for diagnostic and carrier testing for Tay-Sachs and Sandhoff diseases.

NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood:

-This is the recommended test for carrier testing for Tay-Sachs disease and Sandhoff disease.

-Testing begins with hexosaminidase A and total enzyme analysis. If the results are consistent with an affected or carrier for Tay-Sachs disease or Sandhoff disease, next generation sequencing to detect single nucleotide and copy number variants for *HEXA* or *HEXB*, respectively, will automatically be performed on the original specimen.

-This test is appropriate for males and pregnant or nonpregnant females.

NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes:

-This test can be used for diagnosis and carrier testing for Tay-Sachs disease or Sandhoff disease.

-Results for hexosaminidase A and total enzyme analysis are reported with recommendations for additional testing when appropriate. All follow-up testing must be ordered separately on new specimens.

-This test is appropriate for males and pregnant or nonpregnant females.

NAGS / Hexosaminidase A and Total Hexosaminidase, Serum:

-This test can be used for diagnosis and carrier testing for Tay-Sachs disease or Sandhoff disease.

-Results for hexosaminidase A and total enzyme analysis are reported with recommendations for additional testing when appropriate.

-If results indicate normal, indeterminate, or carrier status and the suspicion of Tay-Sachs disease remains high, MUGS / Hexosaminidase A, Serum for Tay-Sachs disease (B1 variant) can typically be added and performed on the same specimen.

-With the exception of MUGS, all follow-up testing must be ordered separately on new specimens.

-This test is **not appropriate** for pregnant females or women receiving hormonal contraception. This test is appropriate for males and nonpregnant females.

-This test is particularly useful when it is difficult to obtain enough blood to perform leukocyte testing (NAGR or NAGW), as may be the case with infants.

MUGS / Hexosaminidase A, Serum:

-This is the recommended test for diagnosis and carrier testing for the B1 variant of Tay-Sachs disease. This test will not detect Sandhoff disease.

-**This test should not be ordered as a first-line test.** Rather, this test should be ordered when the NAGR, NAGW, NAGS indicate normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. In most cases, this test can be performed on the original specimen collected for NAGS.

Shipping Instructions

For optimal isolation of leukocytes, it is recommended the specimen arrive refrigerated within 6 days of collection to be stabilized. Collect specimen Monday through Thursday only and not the day before a holiday. Specimen should be collected and packaged as close to shipping time as possible.

Specimen Required

Container/Tube:

Preferred: Yellow top (ACD solution B)

Acceptable: Yellow top (ACD solution A)

Specimen Volume: 6 mL

Collection Instructions: Send specimen in original tube. **Do not aliquot.**

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing-Spanish](#) (T826)

2. [Biochemical Genetics Patient Information](#) (T602)

3. If not ordering electronically, complete, print, and send an [Inborn Errors of Metabolism Test Request](#) (T798) with the specimen.

Reject Due To

Gross hemolysis Reject

Specimen Minimum Volume

5 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood ACD	Refrigerated (preferred)	6 days	YELLOW TOP/ACD
	Ambient	6 days	YELLOW TOP/ACD

Clinical & Interpretive

Clinical Information

Tay-Sachs and Sandhoff diseases, also referred to as GM2 gangliosidoses, are lysosomal storage disorders 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 and Sandhoff diseases are autosomal recessive conditions. Tay-Sachs disease results from 2 variants in *HEXA*, which encodes for the alpha subunit of hexosaminidase, and causes a deficiency of hexosaminidase A enzyme. An increased carrier frequency for Tay-Sachs disease is observed in individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. Patients with Sandhoff disease have 2 variants in *HEXB*, which encodes for the beta subunit of hexosaminidase, and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes. Sandhoff disease does not exhibit an increased carrier frequency in any specific population.

Clinical Phenotypes:

Phenotypically, patients with Tay-Sachs and Sandhoff diseases are clinically indistinguishable. Variability is observed with respect to age of onset and clinical symptoms. Enzyme analysis is generally required to distinguish between the 2 disorders.

The acute infantile forms of Tay-Sachs and Sandhoff diseases typically present 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 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age.

The juvenile or subacute forms often present between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death typically occurs 2 to 4 years later.

Disease progression is slower in patients with chronic or adult-onset Tay-Sachs and Sandhoff diseases. 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, 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.

Testing Options:

Several tests are available for the detection of carriers of, and individuals affected with, Tay-Sachs and Sandhoff diseases (see Table and Testing Algorithms). This test is the recommended test for both diagnostic and carrier testing. Testing begins with enzyme analysis and when indicated reflexes to the appropriate molecular analysis (either *HEXA* or *HEXB* gene), which includes next-generation sequencing to detect single nucleotide and copy number variants.

Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier, possible carrier, or affected ranges. This differentiates between nondisease causing pseudodeficiency alleles and disease-causing variants. In addition, molecular analysis allows for the facilitation of carrier testing and prenatal diagnosis for at-risk individuals.

Table

Test ID	Test Name	Tay-Sachs disease		Sandhoff disease		Reflexes to molecular genetic testing	Use during pregnancy or hormonal contraception	Preferred use
		Carrier	Affected	Carrier	Affected			
NAGR	Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood	Yes	Yes	Yes	Yes	Yes	Yes	Diagnostic or carrier testing
NAGW	Hexosaminidase A and Total Hexosaminidase, Leukocytes	Yes	Yes	Yes	Yes	No	Yes	Diagnostic or carrier testing
NAGS	Hexosaminidase A and Total Hexosaminidase, Serum	Yes	Yes	Yes	Yes	No	No	Diagnostic
MUGS*	Hexosaminidase A,	Yes	Yes	No	No	No	No	Diagnostic,

	Serum								secondary only
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*MUGS testing should be utilized only when one of the other assays indicates normal, indeterminate, or carrier results and the clinical suspicion of Tay-Sachs disease remains high.

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

Interpretation

Interpretation is provided with report.

Cautions

A small percentage (<0.5%) of carriers may exhibit normal hexosaminidase A activity and will not be detected by this method.(1)

GM2 activator deficiency (AB variant, *GM2A*) is a rare disorder with clinical features similar to Tay-Sachs and Sandhoff diseases; however, levels of both hexosaminidase A and B are normal. GM2 activator deficiency is not detected with this assay. Molecular genetic analysis of *GM2A* is available, see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Clinical Reference

- [1. Triggs-Raine BL, Feigenbaum ASJ, Natowicz M, et al: Screening for carriers of Tay-Sachs disease among Ashkenazi Jews-A comparison of DNA-based and enzyme-based tests. N Engl J Med. 1990 Jul;323\(1\):6-12](#)
2. Delnooz CCS, Lefeber DJ, Langemeijer SMC, et al: New cases of adult-onset Sandhoff disease with a cerebellar or lower motor neuron phenotype. J Neurol Neurosurg Psychiatry. 2010 Sep;81(9):968-972
3. Vallance H, Morris TJ, Coulter-Mackie M, et al: Common HEXB polymorphisms reduce serum HexA and HexB

enzymatic activities, potentially masking Tay-Sachs disease carrier identification. *Mol Genet Metab.* 2006 Feb;87(2):122-127

4. Toro C, Shirvan L, Tifft C: *HEXA* disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed March 29, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1218/

5. Neudorfer O, Pastores GM, Zeng BJ, et al: Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. *Genet Med.* 2005 Feb;7(2):119-123

6. Sutton VR: Tay-Sachs disease screening and counseling families at risk for metabolic disease. *Obstet Gynecol Clin North Am.* 2002 Jun;29(2):287-296

7. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K: The GM2 gangliosidoses. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. *The Online Metabolic and Molecular Bases of Inherited Disease*. McGraw-Hill. Accessed January 30, 2020. Available at <http://ommbid.mhmedical.com/content.aspx?bookid=2709§ionid=225547784>

8. D'Souza G, McCann CL, Hedrick J, et al: Tay-Sachs disease carrier screening: a 21-year experience. *Genet Test.* 2000;4(3):257-263

Performance

Method Description

Leukocyte hexosaminidase A and total hexosaminidase are estimated using a semiautomated modification of the method of O'Brien, et al (1970) with further specific recommendations on specimen preparation as outlined by the International Tay-Sachs Disease Testing Quality Control and Data Collection Center.(O'Brien JS, Okada S, Chen A, Fillerup DL: Tay-Sachs disease: detection of heterozygotes and homozygotes by hexosaminidase assay. *N Engl J Med.* 1970;283:15-20; Cowan T, Pasquali M: Laboratory investigations of inborn errors of metabolism. In: Sarafoglou K, Hoffman GF, Roth KS, eds. *Pediatric Endocrinology and Inborn Errors of Metabolism*. 2nd ed. McGraw-Hill; 2017:1139-1158)

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the gene analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the gene analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

WBC homogenate: 1 month

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

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 US Food and Drug Administration.

CPT Code Information

83080 x2

81406 (if appropriate)

81479 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NAGR	Hexosaminidase A and Tot, WBC/Mole	87543-5

Result ID	Reporting Name	LOINC®
8775	Hexosaminidase Total, WBC	24075-4
2294	Hexosaminidase Percent A, WBC	23825-3
2284	Interpretation (NAGW)	59462-2
35029	Reviewed By	18771-6