

Overview

Useful For

Carrier detection and diagnosis of Tay-Sachs disease

Carrier detection and diagnosis of Sandhoff disease

Testing Algorithm

For more information 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 \(Spanish\)](#)

Method Name

Heat Inactivation, Fluorometric, Semi-Automated

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD

Ordering Guidance

Testing for Tay-Sachs Disease and Sandhoff Disease

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):

- 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 whole blood 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 a [Biochemical Genetics Test Request](#) (T798) with the specimen.

Specimen Minimum Volume

5 mL

Reject Due To

Gross hemolysis	Reject
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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 result 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 virtually 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, Ordering Guidance, and Testing Algorithm). The recommended test for both diagnostic and carrier testing is NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood. Testing begins with enzyme analysis and when indicated reflexes to the appropriate molecular analysis (either *HEXA* or *HEXB* gene), which includes sequencing and deletion/duplication analysis.

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, Serum	Yes	Yes	No	No	No	No	Diagnostic, secondary only

*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;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;81(9):968-972
3. Vallance H, Morris TJ, Coulter-Mackie M, Lim-Steele J, Kaback M. Common HEXB polymorphisms reduce serum HexA and HexB enzymatic activities, potentially masking Tay-Sachs disease carrier identification. *Mol Genet Metab.* 2006;87(2):122-127
4. Toro C, Shirvan L, Tifft C: *HEXA* disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews* [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1218/
5. Leal AF, Benincore-Florez E, Solano-Galarza D, et al. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. *Int J Mol Sci.* 2020;21(17):6213. Published 2020 Aug 27. doi:10.3390/ijms21176213.
6. 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; 2019. Accessed July 17, 2024. Available at <https://ommbid.mhmedical.com/content.aspx?bookid=2709§ionid=225547784>

Performance

Method Description

Leukocyte hexosaminidase A and total hexosaminidase are estimated using a semi-automated 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[1]:15-20; Cowan T, Pasquali M: Laboratory investigations of inborn errors of metabolism. In: Sarafoglou K, Hoffman GF, Roth KD, eds. *Pediatric Endocrinology and Inborn Errors of Metabolism*. 2nd ed. McGraw-Hill; 2017:1139-1158)

PDF Report

No

Day(s) Performed

Preanalytical processing: Monday through Saturday

Assay performed: Friday

Report Available

2 to 8 days

Specimen Retention Time

White blood cell homogenate: 1 month

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes**Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

83080 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
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NAGW	Hexosaminidase A and Total, WBC	87544-3
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Result ID	Test Result Name	Result LOINC® Value
8775	Hexosaminidase Total, WBC	24075-4
2294	Hexosaminidase Percent A, WBC	23825-3
2284	Interpretation (NAGW)	59462-2
35029	Reviewed By	18771-6