Overview

Useful For

Carrier detection and diagnosis of Tay-Sachs disease

Carrier detection and diagnosis of Sandhoff disease

Genetics Test Information

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:

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

-Testing begins with hexosaminidase A and total enzyme analysis. If the results are consistent with an affected or carrier individual, Tay-Sachs mutation analysis will automatically be performed on the original specimen.

-This is not the recommended test for Sandhoff disease; however, if the results are suggestive of Sandhoff disease or carrier status, this will be indicated in the interpretive comment along with recommendations for additional testing. Follow-up testing for Sandhoff must be ordered separately.

-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 is the recommended test for diagnosis and carrier testing for Sandhoff disease. This test also can be used for diagnosis and carrier testing for Tay-Sachs 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 (TSD) remains high, MUGS / Hexosaminidase A (MUGS), Serum for TSD-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. This test is appropriate for males and nonpregnant females.

-Although a leukocyte test is preferred for Tay-Sachs disease, this test can be used if it is difficult to obtain enough blood to perform testing, as may be the case with infants. Additionally, the biochemical workup for TSD could be completed with MUGS testing without collecting a new specimen.

MUGS / Hexosaminidase A (MUGS), 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 is performed on serum using the natural substrate. It 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.

Testing Algorithm

See Tay-Sachs Disease Carrier Testing Protocol in Special Instructions.

Special Instructions

- Informed Consent for Genetic Testing
- Tay-Sachs Disease Carrier Testing Protocol
- Biochemical Genetics Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Heat Inactivation, Fluorometric, Semi-automated

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD

Shipping Instructions

For optimal isolation of leukocytes, it is recommended the specimen arrive refrigerated within 96 hours of draw to be stabilized. Draw specimen Monday through Thursday only and not the day before a holiday. Specimen should be drawn 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: Do not transfer blood to other containers.

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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Biochemical Genetics Patient Information (T602) in Special Instructions

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

Specimen Minimum Volume

5 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood ACD	Refrigerated (preferred)	4 days	YELLOW TOP/ACD
	Ambient	4 days	YELLOW TOP/ACD

Clinical and Interpretive

Clinical Information

Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, 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 disease is an autosomal recessive condition resulting from 2 mutations in *HEXA,* which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms.

The acute infantile form typically presents 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 age 1. 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 age 5.

The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later.

Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. 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 (loss of speech), 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.

The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles.

Sandhoff disease is an autosomal recessive condition resulting from 2 mutations in *HEXB*, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population.

Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies.

A very small group of patients affected with Tay-Sachs disease have mutations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high.

Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

For additional testing options for Tay-Sachs and Sandhoff disease, see NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes (Tay-Sachs disease only) and NAGS / Hexosaminidase A and Total Hexosaminidase,

Serum (Tay-Sachs and Sandhoff diseases (not appropriate for Sandhoff detection in females who are pregnant or receiving hormonal contraception).

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.

Hexosaminidase A usually composes more than 62% of the total hexosaminidase activity in leukocytes (normal =63%-75% A).

In leukocytes, the percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs disease:

-63% to 75% hexosaminidase A is normal (noncarrier)

-58% to 62% hexosaminidase A is indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for prenatal diagnosis if desired)

-less than 58% hexosaminidase A is a carrier (molecular testing recommended to discern disease-causing mutations from pseudodeficiency alleles and to allow for prenatal diagnosis, if desired)

-less than 20% hexosaminidase A is consistent with a diagnosis of Tay-Sachs disease

In leukocytes, the total hexosaminidase in combination with the percent hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with Sandhoff disease:

-greater than or equal to 76% hexosaminidase A is suggestive of a Sandhoff carrier, when the total hexosaminidase is depressed

-Total hexosaminidase activity near zero with nearly 100% hexosaminidase A is consistent with Sandhoff disease

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 (GM2-gangliosidosis, AB variant) 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 cannot be identified through testing offered at Mayo Clinic Laboratories.

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;323:6-12

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;81:968-972

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. Kaback MM, Desnick RJ. Hexosaminidase A Deficiency. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al. Seattle, WA, University of Washington, Seattle; 1993-2015. 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. 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 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;283:15-20)

PDF Report

No

Day(s) and Time(s) Test Performed

Specimens are stabilized Monday through Sunday

Assay is performed Tuesday, Thursday, and alternating Fridays; 8 a.m. (not reported on Saturday or Sunday)

Analytic Time

4 days

Maximum Laboratory Time

8 days

Specimen Retention Time

WBC homogenate stored 1 month

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

83080 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NAGW	Hexosaminidase A and Total, WBC	87544-3

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