Overview

Useful For
Recommended test for carrier detection and diagnosis of Sandhoff disease (except in instances of females who are pregnant or receiving hormonal contraception)

Carrier detection and diagnosis of Tay-Sachs disease

Genetics Test Information
This test is appropriate for carrier detection and diagnosis of both Sandhoff disease and Tay-Sachs disease in males and females who are neither pregnant nor receiving hormonal contraception. Refer to NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex or NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes for carrier detection and diagnosis of Tay-Sachs disease.

Testing Algorithm
The following algorithms are available in Special Instructions:

- Tay-Sachs Disease Carrier Testing Protocol
- Tay-Sachs and Related Disorders Diagnostic Testing Algorithm

Special Instructions
- Informed Consent for Genetic Testing
- Tay-Sachs Disease Carrier Testing Protocol
- Biochemical Genetics Patient Information
- Tay-Sachs and Related Disorders Diagnostic Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name
Heat Inactivation, Fluorometric, Automated

NY State Available
Yes

Specimen

Specimen Type
Serum

Advisory Information
1. Serum assay results are not valid on pregnant females and will not be run. If carrier screening for Tay-Sachs or Sandhoff disease is desired in a pregnant female and testing was not performed prior to pregnancy, refer to NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex or NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes for testing on the patient or partner.

2. The recommended test for Tay-Sachs carrier screening (regardless of gender or pregnancy status) is NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex.

Specimen Required
Container/Tube:

Preferred: Red top
Acceptable: Serum gel

Specimen Volume: 1 mL

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

0.5 mL

Reject Due To

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<td>Gross lipemia</td>
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<td>Gross icterus</td>
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Specimen Stability Information

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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 the *HEXA* gene, 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 the HEXB gene, 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
NAGS
Hexosaminidase A and Total, S

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.

Reference Values
HEXOSAMINIDASE TOTAL, S
< or =15 years: > or =20 nmol/min/mL
> or =16 years: 10.4-23.8 nmol/min/mL
HEXOSAMINIDASE PERCENT A, S
< or =15 years: 20-90%
> or =16 years: 56-80%

Interpretation
Interpretation is provided with report.

Cautions
This test cannot be performed on pregnant females.

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

Performance
Method Description
The hexosaminidases are among the more active of the lysosomal enzymes, which hydrolyze derivatives of beta-D-N-acetylglucosamine and beta-D-N-acetylgalactosamine. Natural substrates are certain sphingolipids (ie, GM2) in which acetylgalactosamine is the terminal monosaccharide. The two hexosaminidase isoenzymes, A and B, differ in their electrophoretic mobility and heat stability. Hexosaminidase A moves toward the anode and is heat labile, while hexosaminidase B moves toward the cathode and is heat stable.

The procedure is performed using an automated pipetting station and a spectrophotometer. The substrate used is 4-methylumbelliferyl-N-acetyl-beta-D-glucopyranoside (4-MUF-acetamido-2-deoxy-beta-D-glucopyranoside) from which the fluorescent compound, 4-methylumbelliferone, is liberated by both hexosaminidases.

The sample is mixed with citrate phosphate buffer and mixture is separated into 2 tubes. One tube stays at ambient temperature and the other is heated at 51.5 degrees C for 15 minutes. On the automated pipetting station, sample and substrate are pipetted into a microtiter test tube located in a 37 degree C waterbath. The hexosaminidase A fraction is destroyed in the heated sample, leaving only hexosaminidase B to react with the substrate. The unheated sample provides the total hexosaminidase (A and B). Thereaction is stopped with glycine after the 30-minute incubation. Sample intensities are compared to that of a 4-methylumbelliferone standard curve to quantitate both the total and the B fraction. The percentage of the A fraction that was inactivated by heating is calculated based on these results. The difference in heat inactivation is used to fractionate hexosaminidase activities.(O'Brien JF: Lysosomal storage diseases. In Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. Second edition. Philadelphia, PA, WB Saunders Company, 1994 pp 2149-2160)

PDF Report
No

Day(s) and Time(s) Test Performed
Varies; 10 a.m.

Analytic Time
8 days

Maximum Laboratory Time
15 days

Specimen Retention Time
30 days

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**

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