MAYO CLINIC LABORATORIES

# Test Definition: NAGR

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

## Overview

### Useful For

Carrier detection and diagnosis of Tay-Sachs disease

Carrier detection and diagnosis of Sandhoff disease

### Reflex Tests

| Test Id | Reporting Name | Available Separately | Always Performed |
|---|---|---|---|
| HEXBZ | HEXB Gene, Full Gene Analysis | Yes | No |
| CULFB | Fibroblast Culture for Genetic Test | Yes | No |
| HEXAN | HEXA Gene Analysis | Yes | No |
| CULAF | Amniotic Fluid Culture/Genetic Test | Yes | No |
| MATCC | Maternal Cell Contamination, B | Yes | No |

### 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.

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/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 all individuals.

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 all individuals.

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 individuals or those receiving hormonal contraception. This test is appropriate for male and nonpregnant female patients.
-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**. Pre-analytical processing is performed Monday through Friday and Sunday. This test may be canceled if specimens are outside of stability when processing occurs. Collect and package specimens for arrival on days when processing is performed.

## 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 |

## 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 disease-causing variants in *HEXA,* which encodes for the alpha subunit of hexosaminidase and causes a deficiency of hexosaminidase A

enzyme. Sandhoff disease results from 2 disease-causing variants in *HEXB*, which encodes for the beta subunit of hexosaminidase and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes.

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 early childhood.

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). 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 for either the *HEXA* or *HEXB* gene.

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. Testing options

| **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 | Yes | Yes | Yes | Yes | Yes | Yes | Diagnostic or carrier testing |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Blood | | | | | | | |
| 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-Stelle 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, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed October 13, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1218/
5. Neudorfer O, Pastores GM, Zeng BJ, Gianutsos J, Zaroff CM, Kolodny EH. Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. Genet Med. 2005;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;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 October 13, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=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. doi:10.1089/10906570050501470

## 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[1]: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 are 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 disease-causing 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 deletion-insertions (delins) 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-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

### Day(s) Performed

Preanalytical processing: Monday through Friday, Sunday
Assay is 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 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 | 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 |