
Overview

Useful For

As a component of the initial evaluation of a patient presenting with hepatosplenomegaly using dried blood spot specimens

This test is **not suitable for** the identification of carriers.

This test **should not be used** as a monitoring tool for patients with confirmed diagnoses.

Special Instructions

- [Biochemical Genetics Patient Information](#)
- [Blood Spot Collection Card-Spanish Instructions](#)
- [Blood Spot Collection Card-Chinese Instructions](#)
- [Blood Spot Collection Instructions](#)

Highlights

This is a screening test for a select number of lysosomal and lipid storage disorders, including cerebrotendinous xanthomatosis, Gaucher disease, and Niemann-Pick diseases types A, B, and C.

The above conditions may all have hepatosplenomegaly as a presenting sign, making this test a helpful component of a patient's initial evaluation.

Although Fabry disease does not have hepatosplenomegaly as a clinical symptom, it can be identified by this assay as the compound, globotriaosylsphingosine, is detected.

Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Ordering Guidance

This test **should not be used** for monitoring of patients with confirmed diagnoses. If a physician is requesting testing for monitoring purposes, see:

-CTXBS / Cerebrotendinous Xanthomatosis, Blood Spot

-GPSY / Glucopsychosine, Blood Spot

-OXYBS / Oxysterols, Blood Spot

This test's clinical sensitivity and specificity for the identification of Niemann-Pick type C (NPC) is 75% and 89%, respectively. If NPC is strongly suspected, the recommended test is HSMP / Hepatosplenomegaly Panel, Plasma.

Specimen Required**Supplies:**

-Card-Blood Spot Collection (Filter Paper) (T493)

-Card-Postmortem Screening (Filter Paper) (T525)

Container/Tube:

Preferred: Blood Spot Collection card

Acceptable: Whatman Protein Saver 903 filter paper, PerkinElmer (formerly Ahlstrom) 226 filter paper, Munktell filter paper, Postmortem Screening Card, or collected with EDTA, sodium heparin, lithium heparin, or ACD B-containing devices

Specimen Volume: 2 Blood spots

Collection Instructions:

1. Let blood dry completely on filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
2. At least 1 spot should be complete (ie, unpunched).
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.

Additional Information:

1. For collection instructions, see [Blood Spot Collection Instructions](#).
2. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777).
3. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800).

Forms

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

2. If not ordering electronically, complete, print, and send a [Biochemical Genetics Test Request](#) (T798) with the specimen.

Reject Due To

Shows serum rings Reject
Insufficient specimen
Layering
Multiple applications

Specimen Minimum Volume

1 Blood spot

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Refrigerated (preferred)	10 days	FILTER PAPER
	Frozen	59 days	FILTER PAPER
	Ambient	10 days	FILTER PAPER

Clinical & Interpretive**Clinical Information**

Hepatosplenomegaly is a presenting or accompanying feature for many different inborn errors of metabolism. It typically is a consequence of chronic hepatic dysfunction or abnormal storage of lipids, sugars, or other improperly metabolized analytes due to a particular enzymatic deficiency. The diagnosis can occasionally be narrowed down by consideration of clinical symptoms; however, clinical diagnosis can be difficult due to similarity of clinical features across disorders, as well as phenotypic variability. Therefore, screening tests can play an important role in the workup of a patient presenting with hepatosplenomegaly who may have a lysosomal or lipid storage disorder.

The conditions detected in this assay are cerebrotendinous xanthomatosis, Gaucher disease, and Niemann-Pick disease types A, B, and with a lower sensitivity and specificity C.

Patients with abnormal results should have follow-up enzymatic or molecular testing for confirmation of diagnosis.

Table. Conditions Identifiable by Method

Disorder	Onset	Analyte detected	Gene	Incidence
Cerebrotendinous xanthomatosis (CTX)	Infancy-adult hood	7-Alpha-hydroxy-4-cholest en-3-one (7a-C4)	CYP27A1	1 in 50,000 As high as 1 in 400 in Druze population.
		7-alpha,12-alpha-dihydrox ycholest-4-en-3-one (7a12aC4)		
Phenotype: early onset diarrhea, cataracts, tendon/cerebral xanthomas, osteoporosis, neuropsychological manifestations, liver disease/hepatosplenomegaly.				
Gaucher disease	Type I: childhood/ad ult	Glucopsychosine (GPSY)	GBA	Type I: 1 in 30,000 to 1 in 100,000
	Types II/III: neonatal-earl y childhood			Types II/III: 1 in 100,000
Phenotype: all types exhibit hepatosplenomegaly and hematological abnormalities. Type I: organomegaly, thrombocytopenia, and bone pain. Absence of neurologic symptoms. Types II/III: primary neurologic disease, developmental delay/regression, hepatosplenomegaly, lung disease. Patients with Type II typically die by age 2 to 4. Patients with Type 3 may have a less progressive phenotype and may survive into				
Niemann-Pick type A/B (NPA/NPB)	NPA: neonatal	Lyso-sphingomyelin (LSM)	SMPD1	Combined incidence 1 in 250,000
	NPB: birth-adultho od	lyso-sphingomyelin 509 (LSM 509)		
Phenotype:				

	<p>NPA: feeding difficulties, jaundice, hepatosplenomegaly, neurologic deterioration, lung disease, hearing and vision impairment, cherry red macula, death usually by age 3.</p> <p>NPB: mainly limited to visceral symptoms; hepatosplenomegaly, stable liver dysfunction, pulmonary compromise, osteopenia.</p>			
Niemann-Pick Type C(NPC)	Variable	Cholestane-3-beta, 5-alpha, 6-beta-triol (COT)	<i>NPC1 or NPC2</i>	1 in 120,000 to 1 in 150,000
	(perinatal-adulthood)	lyso-sphingomyelin 509 (LSM 509)		
Phenotype: Variable clinical presentation. Ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, seizures, +/- hepatosplenomegaly.				

Patients with Fabry disease may also be identified by this assay. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. Normal values of LGb3 do not rule-out Fabry disease. Patients with Fabry disease do not have hepatosplenomegaly as an accompanying feature.

Reference Values
CHOLESTANE-3-BETA, 5-ALPHA, 6-BETA-TRIOL

Cutoff: < or =0.800 nmol/mL

LYSO-SPHINGOMYELIN

Cutoff: < or =0.100 nmol/mL

GLUCOPSYCHOSINE

Cutoff: < or =0.040 nmol/mL

7-ALPHA-HYDROXY-4-CHOLESTEN-3-ONE (7a-C4)

Cutoff: < or =0.750 nmol/mL

7-ALPHA,12-ALPHA-DIHYDROXYCHOLEST-4-en-3-ONE (7a12aC4)

Cutoff: < or =0.250 nmol/mL

GLOBOTRIAOSYLSPHINGOSINE

Cutoff: < or =0.034 nmol/mL

Interpretation

An elevation of 7-alpha-hydroxy-4-cholesten-3-one and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one is strongly suggestive of cerebrotendinous xanthomatosis.

An elevation of lyso-sphingomyelin and lyso-sphingomyelin 509 is highly suggestive of Niemann-Pick type A or B disease.

An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol) lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick disease type C.

An elevation of glucopsychosine is indicative of Gaucher disease.

Cautions

Patients with Wolman disease or cholestatic biliary atresia may have a profile similar to Niemann-Pick disease type C

Patients with bile acid malabsorption or ileal resection may have elevations of 7-alpha-hydroxy-4-cholesten-3-one

This test does not identify all causes of hepatosplenomegaly.

A positive test result is strongly suggestive of a diagnosis but needs follow-up by stand-alone biochemical or molecular assay.

Clinical Reference

1. DeBarber AE, Luo J, Star-Weinstock M, et al: A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. *J. Lipid Res.* 2014 Jan;55(1):146-154
2. Federico A, Dotti MT, Gallus GN: Cerebrotendinous xanthomatosis. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2003. Updated April 14, 2016. Accessed November 20, 2020.

Available at www.ncbi.nlm.nih.gov/books/NBK1409/

3. Grabowski GA, Petsko GA, Phil D, Kolodny EH: Gaucher disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed February 4, 2021. Available at <https://ommbid.mhmedical.com/content.aspx?sectionid=225546056&bookid=2709>
4. Murugesan V, Chuan WL, Liu J, et al: Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016 Nov;91(11):1082-1089
5. Patterson M: Niemann-Pick disease type C. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated August 29, 2019. Accessed February 4, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1296/

Performance

Method Description

A 3-mm dried blood spot is extracted with internal standard. The extract is subjected to liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis. The MS/MS is operated in the multiple reaction monitoring positive mode to follow the precursor to product species transitions for each analyte and internal standard. The ratio of the extracted peak areas to internal standard is determined by LC-MS/MS is used to calculate the concentration of in the sample.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

Normal result: 2 months; Abnormal result: Indefinitely

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

82542

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HSMBS	Hepatosplenomegaly Panel, BS	92745-9

Result ID	Reporting Name	LOINC®
601526	Interpretation (HSMBS)	59462-2
601520	Cholestane-3beta,5alpha,6beta-triol	92757-4
601521	Lyso-sphingomyelin	92749-1
601522	Glucopsychosine	92752-5
601523	7a-hydroxy-4-cholesten-3-one	92763-2
601524	7a,12a-dihydroxycholest-4-en-3-one	92760-8
601525	Globotriaosylsphingosine	92754-1
601527	Reviewed By	18771-6