MAYO CLINIC LABORATORIES

Test Definition: PLSD

Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot

Overview

Useful For

Evaluation of patients with a clinical presentation suggestive of a lysosomal storage disorder, specifically Gaucher, Niemann-Pick type A or type B, Pompe, Krabbe, or Fabry disease, or mucopolysaccharidosis I; or a peroxisomal disorder, either X-linked adrenoleukodystrophy or Zellweger spectrum disorders

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
MPSBS	Mucopolysaccharidosis, BS	Yes	No
PSY	Psychosine, BS	Yes	No
GPSY	Glucopsychosine, BS	Yes	No
OXYBS	Oxysterols, BS	Yes	No
LPCBS	LysoPC by LC MS/MS, BS	Yes	No
PDBS	Pompe Disease, BS	Yes	No
LGBBS	Globotriaosylsphingosine, BS	Yes	No

Testing Algorithm

First-tier results will be reviewed, and second-tier screening performed at a clinical biochemical geneticist's discretion at an additional charge. This minimizes the false-positive rate and maximizes the positive predictive value of screening for these disorders.

For more information see:
Newborn Screen Follow up for Fabry Disease
Newborn Screen Follow-up for Gaucher Disease
Newborn Screen Follow-up for Mucopolysaccharidosis Type I
Newborn Screen Follow-up for Pompe Disease
Newborn Screen Follow-up for X-Linked Adrenoleukodystrophy

If the patient has abnormal newborn screening results for XALD or a lysosomal disorder, immediate actions should be taken. Refer to the appropriate ACMG Newborn Screening ACT Sheet.(1)

Special Instructions

- Informed Consent for Genetic Testing
- Biochemical Genetics Patient Information
- Blood Spot Collection Card-Spanish Instructions
- Newborn Screen Follow-up for X-Linked Adrenoleukodystrophy
- Newborn Screen Follow-up for Pompe Disease
- Newborn Screen Follow-up for Mucopolysaccharidosis Type I
- Newborn Screen Follow-up for Gaucher Disease

- Newborn Screen Follow up for Fabry Disease
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions
- Newborn Screen Follow-up for Acid Sphingomyelinase Deficiency

Highlights
This is a screening test performed from a blood spot for a select number of lysosomal and peroxisomal disorders, including Gaucher disease, Fabry disease, Pompe disease, Krabbe disease, Niemann-Pick diseases A and B, mucopolysaccharidosis type I, Zellweger spectrum disorders, and X-linked adrenoleukodystrophy (XALD).

Additional biochemical or molecular testing is required to confirm a diagnosis if enzyme deficiency is detected by this screening test.

Method Name
Flow Injection Analysis Tandem Mass Spectrometry (FIA-MS/MS)

NY State Available
Yes

Specimen

Specimen Type
Whole blood

Ordering Guidance
To evaluate adult patients with a clinical presentation suggestive of adrenomyeloneuropathy, the recommended test is POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum. Lysophosphatidylcholine concentrations may not be consistently elevated in adult blood spots.

Specimen Required
Supplies: Card-Blood Spot Collection (Filter Paper) (T493)
Container/Tube:
Preferred: Blood Spot Collection Card
Acceptable: PerkinElmer 226 filter paper, Munktell filter paper, Whatman Protein Saver 903 paper, local newborn screening card, or blood collected in tubes containing ACD, EDTA, or heparin and dried on acceptable filter paper
Specimen Volume: 2 Blood spots
Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year of age is fingerstick. .See How to Collect Dried Blood Spot Samples via fingerstick.
2. Completely fill at least 2 circles on the filter paper card (approximately 100 microliters blood per circle).
3. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.

4. Do not expose specimen to heat or direct sunlight.
5. Do not stack wet specimens.
6. 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. **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

1 Blood spot

Reject Due To

Blood spot specimen that shows serum rings or has multiple layers	Reject
Insufficient specimen	Reject
Incubated/exposed to temperatures above 37 degrees C	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Refrigerated (preferred)	56 days	FILTER PAPER
	Frozen	56 days	FILTER PAPER
	Ambient	7 days	FILTER PAPER

Clinical & Interpretive

Clinical Information

Lysosomes are intracellular organelles that contain hydrolytic enzymes to degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases where macromolecules accumulate due to either defects in their transport mechanisms across the lysosomal membrane or defective lysosomal enzyme function. Accumulation of these macromolecules in the lysosomes leads to cell damage and, eventually, organ dysfunction. More than 50 lysosomal storage disorders have been described with a wide phenotypic spectrum.

Gaucher disease results from a deficiency of the enzyme, beta-glucosidase caused by variants in the *GBA* gene. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine). There are 3 described types of Gaucher disease with varying clinical presentations and age of onset, from a perinatal lethal disorder to milder, later onset variants. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2.

Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase due to variants in the *SMPD1* gene. This results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of type A versus type B is based on the age of onset as well as the severity of symptoms. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by 3 years of age. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Treatment is supportive, although there are clinical trials in place.

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to variants in the *GAA* gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. The clinical presentation of Pompe disease ranges from a rapidly progressive infantile variant, which is uniformly lethal if untreated, to a more slowly progressive late-onset variant. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Enzyme replacement therapy is available for all variants and should be started as soon as possible for patients with the infantile variant and at the first signs of muscle weakness in the later onset variants.

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by variants in the *GALC* gene resulting in a deficiency of galactocerebrosidase (GALC; galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration, including white matter disease, follows with death usually occurring by 2 years of age. A subset of individuals have later onset forms of the disease, which are characterized by ataxia, vision loss, weakness, and

psychomotor regression. They can present anywhere from age 6 months to the seventh decade of life and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Psychosine has been shown to be elevated in patients with clinical signs and symptoms of disease and, therefore, may be a useful biomarker for the presence of disease or disease progression. The only available therapy is hematopoietic stem cell transplantation, which is best performed prior to the onset of clinical symptoms.

Fabry disease, caused by variants in the *GLA* gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 male patients. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Male patients with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage kidney disease and cardiac and cerebrovascular disease, generally occurs in middle age. Male patients with greater than1% GLA activity may present with a variant form of Fabry disease with onset of symptoms later in life. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end stage kidney disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings, such as cardiomyopathy or mitral insufficiency, in the fourth decade. The cardiac variant is not associated with kidney failure. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Enzyme replacement therapy is a treatment option for both male and female patients with Fabry disease.

Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase (IDUA) enzyme. Reduced IDUA activity results in accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosome. The clinical presentation and severity of symptoms of MPS I are variable, ranging from severe disease to attenuated variants (historically known as Hurler-Scheie disease and Scheie disease) that generally present with a later onset and a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disability or learning difficulties, and cardiac valvular disease. MPS-I is caused by genetic variants in the *IDUA* gene and has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy.

Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids, alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects, such as Zellweger spectrum disorders (ZSD) are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy (XALD), the organelle is intact but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to milder, later onset variants.

XALD is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 male patients. A defect in the *ABCD1* gene is responsible for the disease. XALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in male patients can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and

asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and is very rare after age 40. It is estimated that approximately 50% of heterozygous individuals are symptomatic and develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

ZSD are a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSD is 1 in 50,000. ZSD follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSD, with approximately 60% to 70% of variants occurring in *PEX1*. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, and hearing loss, and have a much slower disease progression. There is no specific treatment for ZSD.

Reference Values

Disease	Marker	Normal range
Gaucher	Acid beta-glucosidase	> or =1.75 nmol/mL/hr
Niemann-Pick A/B	Sphingomyelinase	> or =2.5 nmol/mL/hr
Pompe	Acid alpha-glucosidase	> or =3.0 nmol/mL/hr
Krabbe	Galactocerebrosidase	> or =0.4 nmol/mL/hr
Fabry	Alpha-galactosidase	> or =2.75 nmol/mL/hr
MPS I	Alpha-L-iduronidase	> or =2.0 nmol/mL/hr
NA	C20 Lysophosphatidylcholine	< or =1.00 mcg/mL
NA	C22 Lysophosphatidylcholine	< or =0.25 mcg/mL
ALD/PBD/ALDH	C24 Lysophosphatidylcholine	< or =0.30 mcg/mL
ALD/PBD/ALDH	C26 Lysophosphatidylcholine	< or =0.30 mcg/mL

Interpretation

When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

Cautions

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

Carrier status (heterozygosity) for these conditions cannot be reliably detected.

Clinical Reference

1. ACMG Newborn Screening ACT Sheets. Accessed August 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508
2. Reuser AJ, Verheijen FW, Bali D, et al. The use of dried blood spot samples in the diagnosis of lysosomal storage disorders--current status and perspectives. Mol Genet Metab. 2011;104(1-2):144-148. doi:10.1016/j.ymgme.2011.07.014
3. Klouwer FCC, Ferdinandusse S, van Lenthe H, et al. Evaluation of C26:0-lysophosphatidylcholine and C26:0-carnitine as diagnostic markers for Zellweger spectrum disorders. J Inherit Metab Dis. 2017;40(6):875-881. doi:10.1007/s10545-017-0064-0
4. Huffnagel IC, van de Beek MC, Showers AL, et al. Comparison of C26:0-carnitine and C26:0-lysophosphatidylcholine as diagnostic markers in dried blood spots from newborns and patients with adrenoleukodystrophy. Mol Genet Metab. 2017;122(4):209-215
5. Part 15 Peroxisomes. 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 August 30, 2023. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419
6. Part 16 Lysosomal disorders. 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 August 30, 2023. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419

Performance

Method Description

Two 1/8-inch dried blood spots (DBS) are excised from a single specimen. The enzymes are extracted by incubating the specimens with a mix of substrate and internal standard for acid sphingomyelinase, beta-glucocerebrosidase, alpha-glucosidase, alpha-galactosidase, galactocerebrosidase, and alpha-L-iduronidase. The sample is then purified by liquid-liquid extraction. The second DBS is extracted with methanol containing d4-C26 lysophosphatidylcholine. The resulting extracts are then combined, evaporated, and reconstituted before analysis by tandem mass spectrometry.(Tortorelli S, Turgeon C, Gavrilov D, et al: Simultaneous testing for 6 lysosomal storage disorders and X-adrenoleukodystrophy in dried blood spots by tandem mass spectrometry. Clin Chem. 2016;62[9]:1248-1254)

PDF Report

No

Day(s) Performed

Monday through Sunday

Report Available

2 days

Specimen Retention Time

6 months

Performing Laboratory Location
Rochester

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

83789

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PLSD	Lysosomal/Peroxisomal D/O Scrn, BS	In Process

Result ID	Test Result Name	Result LOINC® Value
34811	Acid Beta-Glucosidase	55917-9
34812	Sphingomyelinase	62316-5
34813	Acid Alpha-Glucosidase	55827-0
34814	Galactocerebrosidase	62310-8
34815	Alpha-Galactosidase	55908-8
34816	Alpha-L-Iduronidase	55909-6
34817	C20 Lysophosphatidylcholine	90920-0
34818	C22 Lysophosphatidylcholine	90921-8
34819	C24 Lysophosphatidylcholine	90922-6
34820	C26 Lysophosphatidylcholine	90923-4
34821	Interpretation (PLSD)	62301-7
34822	Reviewed By	18771-6
620785	Iduronate 2-Sulfatase	79462-8