Test Definition: LDALD

LSD/X-ALD Newborn Screen, BS

Overview

Useful For

First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, mucopolysaccharidosis I (MPS-I), Niemann-Pick types A and B, and Pompe (glycogen storage disorder type II)

First-tier newborn screen for the peroxisomal disorder: X-linked adrenoleukodystrophy; may also detect Zellweger spectrum disorders

This test is supplemental and **not intended to** replace state-mandated newborn screening.

Test is **not intended for** metabolic screening of symptomatic patients.

Genetics Test Information

Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules leading to cell damage and organ dysfunction.

Peroxisomal disorders such as X-linked adrenoleukodystrophy are caused by a defect in a single peroxisomal enzyme/transporter, whereas Zellweger syndrome spectrum (ZSS) disorders are caused by peroxisome biogenesis defects.

Due to the improved outcomes associated with presymptomatic intervention, some states have recently added select lysosomal storage disorders and peroxisomal disorders to their newborn screening programs.

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

Testing Algorithm

First-tier results will be reviewed and second-tier screening performed at a clinical biochemical geneticist's discretion at no additional charge. This minimizes the false-positive rate and maximizes the positive predictive value of screening for these lysosomal storage disorders.

The following algorithms are available in Special Instructions:

-Newborn Screen Follow-up for Gaucher Disease

-Newborn Screen Follow-up for Mucopolysaccharidosis Type I

-Newborn Screen Follow-up for Niemann Pick Type A and B

-Newborn Screen Follow-up for Pompe Disease

-Newborn Screen Follow-up for X-Linked Adrenoleukodystrophy

For more information, see the following Newborn Screening ACT Sheets:

-Newborn Screening Act Sheet Fabry Disease: Decreased Alpha-Galactosidase A

-Newborn Screening Act Sheet Gaucher Disease: Decreased Acid Beta-Glucosidase

-Newborn Screening Act Sheet Krabbe Disease: Decreased Galactocerebrosidase

-Newborn Screening Act Sheet Mucopolysaccharidosis Type I: Decreased Alpha-L-Iduronidase

-Newborn Screening Act Sheet Niemann-Pick A/B Disease: Decreased Acid Sphingomyelinase

-Newborn Screening Act Sheet Pompe Disease: Decreased Acid Alpha-Glucosidase

-Newborn Screening Act Sheet X-Linked Adrenoleukodystrophy: Increased Very Long Chain Fatty Acids

Special Instructions

- Biochemical Genetics Patient Information
- Blood Spot Collection Card-Spanish Instructions
- Newborn Screening Act Sheet Fabry Disease: Decreased Alpha-Galactosidase A
- Newborn Screening Act Sheet Gaucher Disease: Decreased Acid Beta-Glucosidase
- Newborn Screening Act Sheet Krabbe Disease: Decreased Galactocerebrosidase
- Newborn Screening Act Sheet Mucopolysaccharidoses Type I: Decreased Alpha-L-Iduronidase
- Newborn Screening Act Sheet Niemann-Pick A/B Disease: Decreased Acid Sphingomyelinase
- Newborn Screening Act Sheet Pompe Disease: Decreased Acid Alpha-Glucosidase
- Newborn Screening Act Sheet X-linked Adrenoleukodystrophy: Increased Very Long Chain Fatty Acids
- Newborn Screen Follow-up for X-Linked Adrenoleukodystrophy
- Newborn Screen Follow-up for Pompe Disease
- Newborn Screen Follow-up for Niemann Pick Type A and B
- Newborn Screen Follow-up for Mucopolysaccharidosis Type I
- Newborn Screen Follow-up for Gaucher Disease
- Blood Spot Collection Card-Chinese Instructions

- Blood Spot Collection Instructions

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Ordering Guidance

Testing performed in the context of newborn screening only. For diagnostic testing, or at a clinical biochemical geneticist's discretion, testing may be changed to PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot.

Necessary Information

Birth weight, time of birth, and gestational age are required.

Specimen Required

Patient must be older than 24 hours and less than 1 week of age.

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

Container/Tube:

Preferred: Card-Blood Spot Collection (Filter Paper)

Acceptable: PerkinElmer 226 (formerly Ahlstrom 226) filter paper, Munktell filter paper, Whatman Protein Saver 903 Paper, or blood collected in tubes containing ACD, EDTA, or heparin and then spotted and dried on 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 Dried Blood Spot Collection Tutorial for how to collect blood spots via fingerstick: https://vimeo.com/508490782 .

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 in Special Instructions.

2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777) in Special Instructions.

3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800) in Special Instructions.

Forms

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

2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-General Request (T239)

-Biochemical Genetics Test Request (T798)

Reject Due To

Shows serum rings	Reject
Insufficient specimen	
Layering	
Multiple applications	
Incubated/Exposed to temperatures above 37 degrees C	

Specimen Minimum Volume

Blood spot: 1

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 that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and, eventually, organ dysfunction. More than 50 lysosomal storage disorders have been described with a wide phenotypic spectrum.

Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine). Gaucher disease is caused by variants in the *GBA* gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to an asymptomatic type. 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 types A and B are caused by a deficiency of sphingomyelinase due to variants in the *SMPD1* gene. The result is 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 and characterized by early onset with feeding problems, dystrophy, persistent jaundice, cherry red maculae, 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 on bone marrow biopsy. The combined prevalence of the 2 types is estimated to be 1 in 250,000. 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 disease 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. Patients with this early infantile onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Molecular genetic analysis of the *GALC* gene may provide information on expected age of first symptoms. 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 that is best performed prior to the onset of clinical symptoms. Early infantile Krabbe disease must, therefore, be considered a critical, time-sensitive newborn screening condition.

Fabry disease, caused by variants in the *GLA* gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). 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. Males 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 renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with more than 1% GLA activity may present with a variant form of Fabry disease. 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. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Pseudodeficiency alleles may also be detected by newborn screening. Treatment with enzyme replacement therapy (ERT) is available for both males and females with Fabry disease.

Mucopolysaccharidosis I (MPS-I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase 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, mental retardation or learning difficulties, and cardiac valvular disease. MPS-I is caused by 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 perform essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), 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 syndrome (ZSS), are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants.

X-linked adrenoleukodystrophy (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 males. At least 50% of all female patients who are heterozygotes for XALD are symptomatic. A defect in the *ABCD1* gene is responsible for the disease. XALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males 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 it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

ZSS is 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 ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations 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, hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. Although ZSS disorders are not a primary disease target for testing, this test will detect infants with these disorders.

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

The quantitative measurements of informative metabolites and related ratios and their bioinformatic evaluation using the Collaborative Laboratory Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn screen

specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics.

The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all listed groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn's results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

Cautions

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

A positive test result is strongly suggestive of a diagnosis but requires follow-up by stand-alone biochemical or molecular assay, which is best coordinated by local genetics providers.

Some cases with milder or later onset disease may not display sufficiently abnormal results during the newborn period and, therefore, yield false-negative results.

Clinical Reference

1. DeJesus VR, Zhou H, Vogt RF, Hannon WH: Changes in solvent composition in tandem mass spectrometry multiplex assay for lysosomal storage disorders do not affect assay results. Clin Chem. 2009;55(3):596-598

2. 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 Nov;40(6):875-881. doi: 10.1007/s10545-017-0064-0.3. 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 Dec;122(4):209-215. doi: 10.1016/j.ymgme.2017.10.012

5. Part 16 Lysosomal disorders. In: Valle D, Beaudet AL, Vogelstein B, Antonarakis SE, et al, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill Education; 2019. Accessed September 28, 2020. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419

6. Orsini JJ, Martin MM, Showers AL, et al: Lysosomal storage disorder 4+1 multiplex assay for newborn screening using tandem mass spectrometry: Application to a small-scale population study for five lysosomal storage disorders. Clin Chim Acta. 2012;413:1270-1273

7. Minter Baerg M, Stoway SD, Hart J, et al: Precision newborn screening for lysosomal disorders. Genet Med. 2018 Aug;20(8):847-854. doi: 10.1038/gim.2017.194

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 (ASM), beta-glucocerebrosidase (ABG), alpha-glucosidase (GAA), alpha-galactosidase (GLA), galactocerebrosidase (GALC) and alpha-L-iduronidase (IDUA). The sample is then purified by liquid-liquid extraction. The second DBS is extracted with methanol containing d4-C26 lysophosphatidylcholines (LPC). 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

Specimen Retention Time

6 months

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

83789

LOINC® Information

Test ID	Test Order Name	Order LOINC Value

LDALD	LSD/X-ALD Newborn Screen, BS	85267-3

Result ID	Reporting Name	LOINC®
38521	LSD/X-ALD Newborn Screen Result	85268-1
38520	Reviewed By	18771-6
BG684	Birth Weight (grams, XXXX)	8339-4
BG685	Time of Birth (24hr Time, XX:XX)	57715-5
BG686	Gestational Age (weeks, XX.X)	76516-4