Test Definition: LDALD

Lysosomal and Peroxisomal Disorders
Newborn Screen, Blood Spot

Overview

Useful For

First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, mucopolysaccharidosis I (MPS I) and II (MPS II), infantile neurovisceral or chronic visceral acid sphingomyelinase deficiency, and Pompe (glycogen storage disorder type II)

First-tier newborn screen for the peroxisomal disorder, X-linked adrenoleukodystrophy and 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 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 spectrum disorders are caused by peroxisome biogenesis defects.

Due to the improved outcomes associated with presymptomatic intervention, some states have recently added select lysosomal 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 disorders.

The following algorithms are available:
-Newborn Screen Follow-up for Acid Sphingomyelinase Deficiency
-Newborn Screen Follow-up for Gaucher Disease
-Newborn Screen Follow-up for Mucopolysaccharidosis Type I Decreased Alpha-L-Iduronidase Activity
-Newborn Screen Follow-up for Pompe Disease
-Newborn Screen Follow-up for X-Linked Adrenoleukodystrophy
-Newborn Screening Follow up for Mucopolysaccharidosis Type II: Decreased Iduronate 2-Sulfatase Activity and Elevated Blood Glycosaminoglycans

If the patient has abnormal newborn screening results for X-linked adrenoleukodystrophy or a lysosomal disorder,

immediate actions should be taken. Refer to the appropriate American College of Medical Genetics and Genomics Newborn Screening ACT Sheet.(1)

Special Instructions

- 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 Decreased Alpha-L-Iduronidase Activity
- Newborn Screen Follow-up for Gaucher Disease
- Blood Spot Collection Card-Chinese Instructions
- Blood Spot Collection Instructions
- Newborn Screen Follow-up for Acid Sphingomyelinase Deficiency
- Newborn Screening Follow up for Mucopolysaccharidosis Type II: Decreased Iduronate 2-Sulfatase Activity and Elevated Blood Glycosaminoglycans

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 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 younger than 1 week.

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, or EDTA and then spotted and dried on filter paper
Specimen Volume: 2 Blood spots

Collection Instructions:
1. Completely fill at least 2 circles on the filter paper card (approximately 100 microliters blood per circle).
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
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 1 of the following with the specimen.
-Biochemical Genetics Test Request (T798)
-General Test Request (T239)

Specimen Minimum Volume

1 Blood spot

Reject Due To

Blood spot specimen that shows serum rings or has multiple layers	Reject
Insufficient specimen	Reject
Specimens known to have been exposed to elevated temperature above ambient	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Refrigerated (preferred)	90 days	FILTER PAPER
	Ambient	28 days	FILTER PAPER
	Frozen	90 days	FILTER PAPER

Clinical & Interpretive

Clinical Information

Lysosomes are intracellular organelles that contain hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules 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 disorders have been described with a wide phenotypic spectrum.

Gaucher disease results from a deficiency of the enzyme, beta-glucosidase, due to disease-causing variants in the *GBA1* 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 (ERT), substrate reduction therapy, and chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2.

Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive disorder caused by disease-causing 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. An early-onset form, infantile neurovisceral ASMD (historically known as Niemann-Pick type A) is characterized by early onset feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by 3 years. A later-onset, chronic visceral form of ASMD (historically known as Niemann-Pick type B) 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 available in the form of ERT to help reduce the accumulation of sphingomyelin in the lung, liver, spleen, and other non-central nervous system organs. ERT does not impact the central nervous system.

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 disease-causing 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 form, which is lethal if untreated, to a more slowly progressive late onset form. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. ERT is available for all disease forms and should be started as soon as possible for patients with the infantile form and at the first signs of muscle disease in the later onset forms.

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by disease-causing 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 to 5 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Individuals with juvenile and adult-onset Krabbe disease present later in life, progress more slowly, and may not have consistently abnormal results on early screening tests. 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. The only available therapy is hematopoietic stem cell transplantation (HSCT), which is best performed prior to the onset of clinical symptoms. Infantile Krabbe disease must, therefore, be considered a critical, time-sensitive newborn screening condition.

Fabry disease is an X-linked disorder caused by disease-causing variants in the *GLA* gene resulting in a deficiency of the alpha-galactosidase A (GLA) enzyme. 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 (near) absent 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 occur in middle age. Male patients with residual 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 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 cardiomyopathy or mitral insufficiency, in the fourth decade. The cardiac variant is not associated with kidney failure. Female patients with Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Pseudodeficiency alleles may also be detected by newborn screening. Treatment via ERT is available for all 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 or learning difficulties, and cardiac valvular disease. MPS I is caused by disease-causing variants in the *IDUA* geneTreatment options include HSCT and ERT.

Mucopolysaccharidosis II (MPS II; Hunter syndrome) is an X-linked disorder caused by the deficiency of the iduronate 2-sulfatase (I2S) enzyme due to disease-causing variants in the *IDS* gene. Reduced I2S activity results in accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosome. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic female carriers have been reported. Treatment options include HSCT and ERT.

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, 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.

X-linked adrenoleukodystrophy is an X-linked disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders. XALD is caused by a disease-causing variant in the *ABCD1*. 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 65-80% of heterozygous individuals develop symptoms of an AMN-like phenotype. Treatment options include hormone replacement therapy, HSCT, gene therapy, or symptom management.

Zellweger spectrum disorders are a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most affected individuals present in childhood, but adult patients have been identified. Most ZSDs are inherited in an autosomal recessive pattern. At least 13 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). The phenotypic spectrum and disease severity is broad. There is no specific treatment for ZSD. Although ZSD are not a primary disease target for testing, this test can detect individuals with ZSD.

Reference Values

An interpretive report will be provided.

Interpretation

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 screening 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 individuals with milder or later onset disease may not have sufficiently abnormal results during the newborn period and, therefore, yield negative results.

Clinical Reference

1. ACMG Newborn Screening ACT Sheets. Accessed October 2, 2025. 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
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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;122(4):209-215. doi:10.1016/j.ymgme.2017.10.012
4. 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 October 2, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419
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 October 2, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419
6. Minter Baerg M, Stoway SD, Hart J, et al. Precision newborn screening for lysosomal disorders. Genet Med. 2018;20(8):847-854. doi:10.1038/gim.2017.194
7. Ream MA, Lam WKK, Grosse SD, et al. Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States. Genet Med. 2023:25(2):100330. doi:10.1016/j.gim.2022.10.012

Performance

Method Description

Three 1/8-inch dried blood spots (DBS) are excised from a single specimen. The enzymes are extracted from 2 DBS by incubating the specimens with a mix of substrate and internal standard for acid sphingomyelinase, beta-glucocerebrosidase, alpha-glucosidase, alpha-galactosidase, galactocerebrosidase, alpha-L-iduronidase, and iduronate 2-sulfatase. The sample is then purified by liquid-liquid extraction. The third DBS is extracted with methanol containing d4-C26 lysophosphatidylcholines. 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 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
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
83789

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
LDALD	LSD/X-ALD Newborn Screen, BS	85267-3

Result ID	Test Result Name	Result LOINC® Value
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