Overview

Useful For
Diagnosis of the lysosomal storage disorders: Fabry (in male patients), Gaucher, Krabbe, mucopolysaccharidosis I (MPS I), Niemann-Pick types A and B, and Pompe (glycogen storage disorder type II)
This test is not intended for carrier detection

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.
Due to the improved outcomes associated with presymptomatic intervention, some states have recently added select lysosomal storage disorders to their newborn screening programs.
This test is an enzyme testing panel for individuals with positive newborn screen results or clinical signs and symptoms suspicious for Fabry disease, Gaucher disease, Krabbe disease, mucopolysaccharidosis I, Niemann-Pick A/B disease or Pompe disease. If an enzyme deficiency is detected by this screening test, additional biochemical or molecular testing is required to confirm a diagnosis.

Testing Algorithm
If acid alpha-glucosidase is less than 5.00 nmol/hour/mg protein, then acid alpha-glucosidase will be added and performed at an additional charge.
If galactocerebrosidase is less than 1.88 nmol/hour/mg protein, then galactocerebrosidase will be added and performed at an additional charge.
The following are available in Special Instructions:
- 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 Niemann-Pick Type A and B
- Newborn Screen Follow-up for Pompe Disease
For more information, see the following Newborn Screening ACT Sheets in Special 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: Decreased Acid Sphingomyelinase
- Newborn Screening Act Sheet Pompe Disease: Decreased Acid Alpha-Glucosidase

Special Instructions
- Informed Consent for Genetic Testing
- Biochemical Genetics Patient Information
- 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
Test Definition: LSD6W
Lysosomal (Six) Panel, WBC

- 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
- Newborn Screen Follow-up for Fabry Disease
- Informed Consent for Genetic Testing (Spanish)

Reflex Tests

<table>
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<th>Test Id</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
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<tr>
<td>GAAWR</td>
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<tr>
<td>GALCR</td>
<td>Galactocerebrosidase Reflex, WBC</td>
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Method Name
Flow Injection Analysis-Tandem Mass Spectrometry (FIA-MS/MS)

NY State Available
Yes

Specimen

Specimen Type
Whole Blood ACD

Ordering Guidance
Carrier detection using enzyme levels is unreliable for female patients as results may be within the normal values. Order FABRZ / Fabry Disease, Full Gene Analysis, Varies for testing carrier status.

Shipping Instructions
For optimal isolation of leukocytes, it is recommended the specimen arrive refrigerated within 6 days of collection to be stabilized. Collect specimen Monday through Thursday only and not the day before a holiday. Specimen should be collected and packaged as close to shipping time as possible.

Specimen Required
Container/Tube:
Preferred: Yellow top (ACD solution B)
Acceptable: Yellow top (ACD solution A) or lavender top (EDTA)
Specimen Volume: 6 mL
Collection Instructions: Send 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 in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)
2. Biochemical Genetics Patient Information (T602) in Special Instructions
3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Reject Due To

Gross hemolysis  Reject

Specimen Minimum Volume
2 mL

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<td>Refrigerated (preferred)</td>
<td>6 days</td>
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<tr>
<td></td>
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Clinical & Interpretive

Clinical Information

Lysosomes are intracellular organelles containing 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 40 lysosomal storage disorders have been described with a wide phenotypic spectrum.

Gaucher Disease:
Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, acid beta-glucosidase (glucocerebrosidase) due to variants in the \( GBA \) gene. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine). Impaired enzyme activity results in accumulation of undegraded glucocerebrosides in the lysosome, resulting in organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease with varying presentations and age of onset, but all include hepatosplenomegaly and hematological abnormalities as symptoms. Gaucher disease type I is the most common, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease. In addition, type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and individuals may survive into the third and fourth decade of life. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and chaperone therapy for types 1 and 3 (type 3, subacute neuropathic/juvenile). Currently, only supportive therapy is available for type 2. The biomarker, glucopsychosine, is elevated in symptomatic individuals and supports a diagnosis of Gaucher disease (GPSY / Glucopsychosine, Blood Spot).

Niemann-Pick disease type A and B:
Niemann-Pick disease types A (NPA) and B (NPB) are caused by a deficiency of sphingomyelinase, which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. NPA is more severe than NPB and is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development
of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. NPB is limited to visceral symptoms with survival into adulthood. Some individuals 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. Both NPA and NPB are caused by variants in the \textit{SMPD1} gene. Individuals with NPA and NPB typically have elevation of the oxysterol, lyso-sphingomyelin; cholestane-3 beta, 5 alpha, 6 beta-triol (COT) or 7-ketocholesterol (7-KC) may also be elevated. For more information see OXYBS / Oxysterols, Blood Spot.

Pompe Disease:

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 \textit{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 organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and eventually, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. Because Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, in particular the juvenile and adult-onset forms, is often considered late, if at all, during the evaluation of individuals presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment with enzyme replacement therapy is available making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis.

Krabbe Disease:

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of the enzyme, galactocerebrosidase (GALC), due to variants in the \textit{GALC} gene. GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide, and lactosylsphingosine). In individuals with Krabbe disease, reduced GALC activity results in impaired degradation of these substrates, causing 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 age 2. 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. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, has shown variable benefit. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A have been found. Saposin A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. The biomarker, psychosine (PSY / Psychosine, Blood Spot) has been shown to be elevated in individuals with active Krabbe disease.

Fabry Disease:

Fabry disease, caused by alterations in the \textit{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. 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 renal disease and cardiac and cerebrovascular disease, generally occurs in middle age. Male patients 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 renal 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 renal failure. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of GLA activity is not generally useful for identifying female patients with Fabry disease, as many carriers have normal enzyme activity. Additional studies including molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) are recommended to detect carriers. The biomarkers globotriaosylsphingosine (LGBBS / Globotriaosylsphingosine, Blood Spot) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in individuals with Fabry disease and may aid in the diagnostic evaluation of female patients.

Mucopolysaccharidosis I:
Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The mucopolysaccharides, heparan sulfate and dermatan sulfate, are elevated in affected individuals (MPSBS / Mucopolysaccharidosis, Blood Spot) and support a diagnosis of MPS I. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with 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.

Reference Values
Beta-Glucosidase: ≥3.53 nmol/hour/mg protein
Acid Sphingomyelinase: ≥0.32 nmol/hour/mg protein
Acid Alpha-Glucosidase: ≥5.00 nmol/hour/mg protein
Galactocerebrosidase: ≥1.88 nmol/hour/mg protein
Alpha-Galactosidase: ≥10.32 nmol/hour/mg protein
Alpha-L-Iduronidase: ≥2.06 nmol/hour/mg protein
Acid Alpha-Glucosidase (Reflex): ≥1.50 nmol/hour/mg protein
Galactocerebrosidase (Reflex): ≥0.300 nmol/hour/mg protein

An interpretative report will be provided.

Interpretation
Values below the reference ranges are consistent with a diagnosis of lysosomal storage disorders. 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), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Cautions
Individuals with pseudodeficiency alleles can show reduced enzyme activity with this assay. Carrier status (heterozygosity) for these conditions cannot be reliably detected. Enzyme levels may be normal in individuals receiving enzyme replacement therapy or who have undergone hematopoietic stem cell transplant.
This test can give false-positive acid sphingomyelinase results. OXYBS / Oxysterols, Blood Spot may be ordered as a confirmatory test.

Clinical Reference

Performance

Method Description
The specimens are incubated with a mix of substrate and internal standard for acid sphingomyelinase, beta-glucocerebrosidase, acid alpha-glucosidase, alpha-galactosidase, galactocerebrosidase, and alpha-L-iduronidase. The sample is then purified by liquid-liquid extraction. The extract is evaporated and reconstituted before analysis by tandem mass spectrometry.(Unpublished Mayo method)

PDF Report
No

Specimen Retention Time
WBC homogenate: 1 month

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
82657
82963
83789 (if appropriate for government payers)
82542 (if appropriate)