

Lysosomal Storage Disorders (LSD)

Use

Quantitative measurement of the activity of the enzymes, acid- α -glucosidase (GAA) and α -L-iduronidase (IDUA), in blood specimens dried on filter paper as an aid in screening newborns for the lysosomal storage disorders, Pompe Disease and Mucopolysaccharidosis Type 1 (MPS 1) Disease.

Clinical Significance

Lysosomal storage disorders result from dysfunction, deficiency, or absence of a lysosomal enzyme. Affected individuals are unable to metabolize the disease-specific substrate of the deficient enzyme, leading to its accumulation in the lysosomes within the cells of the body.

Pompe, or glycogen storage disease type II, is a rare and progressive neuromuscular disorder inherited in an autosomal recessive manner. It is characterized by a deficiency or absence of the lysosomal enzyme GAA, which normally cleaves glycogen to form glucose. There are three forms of Pompe that determine the severity of disease and age of onset.

- *Classic infantile-onset Pompe* begins before or shortly after birth with symptoms that include hypotonia (poor muscle tone), failure to thrive, difficulty breathing, trouble feeding, and respiratory infections.
- *Non-classic infantile-onset Pompe* usually presents by age one and affected babies show signs of delayed motor skills, progressive muscle weakness (myopathy), and difficulty breathing.
- *Late-onset Pompe* may develop in childhood, adolescence, or even adulthood. It is also associated with progressive muscle weakness and difficulty breathing. Symptoms are usually milder and progress more slowly.

Infantile forms of Pompe may be fatal within the first year of life, if untreated. Even with treatment, children with either form of infantile-onset Pompe usually pass away in early childhood. Pompe disease diagnosis is confirmed through genetic testing, identifying pathogenic mutations in the *GAA* gene.

Mucopolysaccharidosis Type 1 (MPS 1) is an inherited condition in which complex sugars cannot be broken down in the lysosomes. MPS 1 is a progressive multisystem disorder with features ranging over a wide continuum of severity that may be categorized from severe to attenuated. Age of onset, symptoms, and long-term outcome within this spectrum vary widely. Babies with severe MPS 1 usually develop signs and symptoms within the first year of life and have rapid disease progression. In the attenuated form, symptoms are generally milder and do not appear until later in childhood. Early signs include umbilical or inguinal hernia, macrocephaly, varying degrees of developmental delay and learning disabilities, and hearing loss. Life expectancy is varied, with affected individuals having a reasonably normal life span while severely affected individuals may die before becoming teenagers. The most common cause of death, even with treatment, is heart or respiratory failure. The diagnosis of MPS I is established with detection of deficient activity of the lysosomal enzyme IDUA in combination with elevation of glycosaminoglycan levels and/or identification of biallelic pathogenic variants in the *IDUA* gene.

Further information and ACT Sheets can be found at the OSDH Newborn Screening Program [website](#).

Methodology

Flow Injection-Tandem mass spectrometry (FIA-MS/MS) is used to quantify levels of GAA and IDUA.

- Cases with low levels of GAA are reflexed to 2nd tier biochemical testing for creatine and creatinine ratio and the activity of GAA (PD2T Test), which can differentiate late-onset Pompe disease from false-positive cases such as carriers and pseudodeficiency of GAA enzyme.
- Cases with low levels of IDUA are reflexed to 2nd tier biochemical testing to confirm deficiency of IDUA enzyme activity in blood as well as demonstration of elevation in urinary glycosaminoglycan (GAG) levels.

Specimen Type

See [Guidance for Collection of NBS Dried Blood Spots](#)

Minimum Volume/Size

See [Guidance for Collection of NBS Dried Blood Spots](#)

Collection Instructions

See [Guidance for Collection of NBS Dried Blood Spots](#)

Common Causes for Rejection

See [Guidance for Collection of NBS Dried Blood Spots](#)

Shipping

See [Guidance for Collection of NBS Dried Blood Spots](#)

Turn-around Time

- Within 5 working days of receipt
- Within 7 working days of receipt, if 2nd tier GAGS or PD2T performed

Reference Range

- GAA > 2.5 µmol/L/h
- IDUA > 1.3 µmol/L/h

Reportable Results

- Within Normal Limits
- Outside Normal Limits
- Invalid

Interpretation

- GAA and IDUA
 - Within Normal Limits: Not consistent with Pompe disease or MPS1
- GAA Normal and IDUA Decreased
 - GAGs Negative: Not Consistent with mucopolysaccharidosis type 1 (MPS1)
 - GAGs Positive: Possible mucopolysaccharidosis type 1 (MPS1); immediate referral to clinical genetics recommended
- GAA Decreased and IDUA Normal
 - PD2T Negative: Not Consistent with Pompe Disease
 - GAGs Positive: Possible Pompe Disease; immediate referral to clinical genetics recommended
- GAA Decrease and IDUA Decreased – Invalid; specimen results inconclusive. Submit a new specimen as soon as possible.

Limitations/Interferences

- This is a screening test only. A diagnostic procedure should be used for confirmation of presumptive Pompe and MPS 1 diseases.
- Certain late onset forms of Pompe disorder may have GAA enzymatic activity in the normal range and result in a false negative newborn screening result.

- False positives for Pompe and MPS 1 can result by identifying pseudo deficiencies and carriers.
- Elevated hemoglobin level at 18.0 g/dL increases IDUA activity, which may result in false negative results for MPS 1. Hemoglobin does not interfere at normal (≤ 15 g/dL) levels.
- Glucose levels above 0.25 g/dL can interfere by causing decreased measured GAA activity resulting in false positive results for Pompe disease. Preterm infants typically with very low birthweights have a high risk of hyperglycemia due to glucose infusion.
- Triglyceride (Intralipid®) can interfere by increasing the measured GAA and IDUA activity. Intralipid® ≤ 0.15 g/dL does not interfere with GAA and ≤ 0.30 g/dL does not interfere with IDUA activity. High triglyceride concentrations in newborns due to medication effects or pathological conditions may cause a false negative newborn screening result for a specimen with measured GAA or IDUA activity close to the cut-off values.
- Variables such as hematocrit, prematurity, and age of infants may affect the interpretation of the values produced.
- Specimens improperly collected, processed or transported may result in erroneous results.

CPT Code

82657

Notes

The test for measuring GAA and IDUA is approved for *in vitro* diagnostic use by the U.S. Food and Drug Administration.

Second-tier biochemical tests performed at Mayo Clinic Laboratories 200 First Street SW, Rochester, MN 55905, were developed and performance characteristics determined in a manner consistent with CLIA requirements. The tests have not been cleared or approved by the U.S. Food and Drug Administration.