MAYO CLINIC LABORATORIES

# Test Definition: LSDGP

Lysosomal Storage Disease Gene Panel, Varies

## Overview

### Useful For

Follow up for abnormal biochemical results and confirmation of suspected lysosomal storage disease (LSD)

Establishing a molecular diagnosis for patients with LSD

Identifying variants within genes known to be associated with LSD, allowing for predictive testing of at-risk family members

### Reflex Tests

| Test Id | Reporting Name | Available Separately | Always Performed |
|---|---|---|---|
| CULFB | Fibroblast Culture for Genetic Test | Yes | No |

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 56 genes associated with lysosomal storage disease: *AGA, ARSA, ARSB, ASAH1, ATP13A2, CHIT1, CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSF, CTSK, DNAJC5, FUCA1, GAA, GALC, GALNS, GBA, GFAP, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GRN, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PANK2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1,* and *TPP1*. See Targeted Genes and Methodology Details for Lysosomal Storage Disease Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for lysosomal storage disease.

### Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

For more information see Lysosomal Disorders Diagnostic Algorithm, Part 2

### Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Lysosomal Disorders Diagnostic Algorithm, Part 2
- Blood Spot Collection Instructions
- Targeted Genes and Methodology Details for Lysosomal Storage Disease Gene Panel

### Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing.

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Ordering Guidance

For neuronal ceroid lipofuscinosis, first-tier biochemical testing is available for the 2 most common types of enzyme deficiency; see TPPTL / Tripeptidyl Peptidase 1 and Palmitoyl-Protein Thioesterase 1, Leukocytes.

Testing for the 15 neuronal ceroid lipofuscinosis genes is available separately; see NCLGP / Neuronal Ceroid Lipofuscinosis (Batten Disease) Gene Panel, Varies.

Customization of this panel and single gene analysis for any gene present on this panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

### Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

### Specimen Required

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood
**Container/Tube:** Lavender top (EDTA) or yellow top (ACD)
**Specimen Volume:** 3 mL
**Collection Instructions:**
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Specimen Type:** Skin biopsy

**Supplies:** Fibroblast Biopsy Transport Media (T115)
**Container/Tube:** Sterile container with any standard cell culture media (e.g., minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.
**Specimen Volume:** 4-mm punch
**Specimen Stability Information:** Refrigerated (preferred)/Ambient
**Additional Information:** A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Type:** Cultured fibroblast
**Container/Tube:** T-25 flask
**Specimen Volume:** 2 Flasks
**Collection Instructions:** Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.
**Specimen Stability Information:** Ambient (preferred)/Refrigerated (<24 hours)
**Additional Information:** A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Type**: Blood spot
**Supplies:** Card-Blood Spot Collection (Filter Paper) (T493)
**Container/Tube**:
**Preferred**: Collection card (Whatman Protein Saver 903 Paper)
**Acceptable**: PerkinElmer 226 (formerly Ahlstrom 226) filter paper, or blood spot collection card
**Specimen Volume**: 5 Blood spots
**Collection Instructions:**
1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see How to Collect Dried Blood Spot Samples.
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
**Specimen Stability Information:** Ambient (preferred)/Refrigerated
**Additional Information:**
1. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.
2. For collection instructions, see Blood Spot Collection Instructions
3. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
4. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

**Specimen Type:** Saliva
**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
**Supplies:** Saliva Swab Collection Kit (T786)
**Specimen Volume:** 1 Swab
**Collection Instructions:** Collect and send specimen per kit instructions.
**Specimen Stability Information:** Ambient 30 days
**Additional Information:** Due to lower concentration of DNA yielded from saliva, it is possible that additional specimen

may be required to complete testing.

### 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. Molecular Genetics: Biochemical Disorders Patient Information (T527)
3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

### Specimen Minimum Volume

See Specimen Required

### Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

### Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Varies | Varies | | |

## Clinical & Interpretive

### Clinical Information

Lysosomal storage diseases (LSD) encompass a group of over 40 inherited biochemical diseases in which genetic variants cause defective lysosomal functioning. Lysosomes perform catabolic functions for cells, which is accomplished through activity of various proteins such as lysosomal enzymes, transport proteins, and other proteins. Functional deficits in these proteins cause an accumulation of substrates in cells leading to progressive organ dysfunction.

This leads to variable clinical features that can affect the cardiovascular, neurological, ocular, and skeletal systems, among others. Clinical features are dependent on the amount and location of the substrate accumulation but may include the following: characteristic facial features (coarse features), hepatomegaly, deafness, vision loss, abnormal skeletal findings, hydrops fetalis, ataxia, hypotonia, developmental delay/regression, and intellectual disability. Age of onset is variable, with symptoms presenting from the prenatal period to adulthood, but generally LSD are progressive and cause significant morbidity and mortality with a decreased lifespan. Enzyme replacement therapy and oral substrate inhibitors are therapeutic options for some LSD.

LSD are inherited in an autosomal recessive manner with the exception of Hunter, Fabry, and Danon diseases, which are X-linked. There are founder variants associated with LSD in the Ashkenazi Jewish and Finnish populations, leading to an increased carrier frequency for some. Overall, the prevalence of LSD is estimated at 1 in 7000 to 1 in 8000.

Neuronal ceroid lipofuscinoses (NCL) are a subset of LSD that involve defective cellular processing of lipids. NCL are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophilic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles

(FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms.

Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult-onset form (ANCL; *DNAJC5* gene) has been shown to be autosomal dominant.

This panel includes sequencing of 43 genes related to various LSD, as well as 15 genes specific to NCL.

Alterations in various genes on this panel have also been associated with Parkinson disease or Lewy body disease. These alterations are not reported for individuals younger than 18 years of age but are available upon request.

## Reference Values

An interpretive report will be provided.

## Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

## Cautions

Clinical Correlations:
Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of at least one reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options, for assistance in general test selection, or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis: This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For detailed information regarding gene specific performance and technical limitations, see Technical Limitations section or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics and Association for Molecular Pathology recommendations as a guideline.(1) Other gene specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

## Clinical Reference

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424
2. Wang RY, Bodamer OA, Watson MS, Wilcox WR; ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011;13(5):457-484

3. Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Ann Rev Med. 2015;66:471-486
4. Filocamo, M. Morrone A. Lysosomal storage disorders: Molecular basis and laboratory testing. Hum Genomics. 2011;5:156-169
5. Coutinho MF, Alves S. From rare to common and back again: 60 years of lysosomal dysfunction. Mol Genet Metab. 2016;117(2):53-65
6. Robak LA, Jansen IE, van Rooij J, et al. Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. Brain. 2017;140(12):3191-3203

## Performance

### Method Description

Next-generation sequencing (NGS) and Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated to be over 99% for single nucleotide variants, over 94% for deletions/insertions (delins) less than 40 base pairs (bp), and over 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Lysosomal Storage Disease Gene Panel for details regarding the targeted genes analyzed and specific gene regions not routinely covered.(Unpublished Mayo method)

Genes analyzed: *AGA, ARSA, ARSB, ASAH1, ATP13A2, CHIT1, CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSF, CTSK, DNAJC5, FUCA1, GAA, GALC, GALNS, GBA, GFAP, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GRN, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PANK2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1,* and *TPP1*

### PDF Report

Supplemental

### Day(s) Performed

Varies

### Report Available

21 to 35 days

### Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Blood spots: 1 month; Saliva: 1 month

### Performing Laboratory Location

## 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

81443
88233-Tissue culture, skin, solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| LSDGP | LSD Gene Panel | 105263-8 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 608536 | Test Description | 62364-5 |
| 608537 | Specimen | 31208-2 |
| 608538 | Source | 31208-2 |
| 608539 | Result Summary | 50397-9 |
| 608540 | Result | 82939-0 |
| 608541 | Interpretation | 69047-9 |
| 608542 | Resources | 99622-3 |
| 608543 | Additional Information | 48767-8 |
| 608544 | Method | 85069-3 |
| 608545 | Genes Analyzed | 48018-6 |
| 608546 | Disclaimer | 62364-5 |
| 608547 | Released By | 18771-6 |