Overview

Useful For

Follow up for abnormal biochemical results and confirmation of suspected lysosomal storage diseases, neuronal ceroid lipofuscinoses (Batten disease), peroxisomal disorders, or glycogen storage diseases

Identifying mutations within genes known to be associated with lysosomal storage diseases, neuronal ceroid lipofuscinoses (Batten disease), peroxisomal disorders, or glycogen storage diseases, allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing and Sanger sequencing to evaluate the genes on this panel including detection of large deletions and duplications.

This ordered service includes the option for 1 of the following metabolic panels:

-Lysosomal Storage Disease Panel (58 genes)

-Neuronal Ceroid Lipofuscinosis (Batten Disease) Panel (15 genes)

-Peroxisomal Disorder Panel (30 genes)

-Glycogen Storage Disease Panel (26 genes)

-Custom Gene Panel (https://orders.mayocliniclabs.com/en/tools/gene_panels)

-Custom Gene Ordering tutorial: https://vimeo.com/299737728/23d56922f1

Risk alleles for Parkinson disease with no known enzyme reduction or lysosomal storage disease association will only be reported in patients over 18 years old. Polymorphisms are available upon request for all patients.

See Targeted Genes for Lysosome, Peroxisome, GSD Panels in Special Instructions for details regarding the targeted genes for each test.

Highlights

This test uses next-generation sequencing to test for variants, including large deletions and duplications, in the genes indicated.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling for lysosomal storage disease, neuronal ceroid lipofuscinoses (Batten disease), peroxisomal disorders, or glycogen storage disease.

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No
G158	Lysosomal Storage Disease Panel	No, (Bill Only)	No

Test ID	Reporting Name	Available Separately	Always Performed
G159	NCL (Batten Disease) Panel	No, (Bill Only)	No
G160	Peroxisomal Disorder Panel	No, (Bill Only)	No
G161	Glycogen Storage Disease Panel	No, (Bill Only)	No
G145	Hereditary Custom Gene Panel Tier 1	No, (Bill Only)	No
G146	Hereditary Custom Gene Panel Tier 2	No, (Bill Only)	No
G147	Hereditary Custom Gene Panel Tier 3	No, (Bill Only)	No
G148	Hereditary Custom Gene Panel Tier 4	No, (Bill Only)	No
G149	Hereditary Custom Gene Panel Tier 5	No, (Bill Only)	No

Testing Algorithm

See Advisory Information for recommended first-tier biochemical testing.

If skin biopsy is received, fibroblast culture will be added and charged separately.

This test includes the option for either 1 of several predefined panel tests or the option to create a custom gene panel. Pricing for the Custom Gene Panel will be based on the number of genes selected (1, 2-14, 15-49, 50-100, and 101-500).

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes for Lysosome, Peroxisome, GSD Panels

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS)/Polymerase Chain Reaction (PCR)/qPCR/Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

For neuronal ceroid lipofuscinosis: First-tier biochemical testing is available for the 2 most common types of

enzyme deficiency: TPPTL / Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Leukocytes.

For peroxisomal disorders: Preliminary biochemical testing may be helpful in making a diagnosis. See POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

The specific metabolic panel desired must be identified in order to perform this test.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Cultured fibroblasts

Container/Tube: T-75 or T-25 flask

Specimen Volume: 1 Full T-75 or 2 full T-25 flasks

Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours

Specimen Type: Skin biopsy

Supplies: Fibroblast Biopsy Transport Media (T115)

Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin. Tubes can be supplied upon request; Eagle's minimum essential medium with 1% penicillin and streptomycin.

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

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. Molecular Genetics: Biochemical Disorders Patient Information (T527) in Special Instructions

Specimen Minimum Volume

Blood: 1 mL

Reject Due To

No specimen should be rejected.

Specimen Stability Information

Specimen Type	Temperature	Time
Varies	Varies	

Clinical and Interpretive

Clinical Information

Lysosomal Storage Disease Panel

Lysosomal storage diseases (LSD) encompass a group of over 40 inherited biochemical diseases in which genetic mutations 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. Some founder mutations have been associated with particular LSD in the Ashkenazi Jewish and Finnish populations, leading to an increased carrier frequency for some. Overall, the prevalence of LSD is estimated at 1/7000 to 1/8000.

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.

Neuronal Ceroid Lipofuscinosis (Batten Disease) Panel

Neuronal ceroid lipofuscinoses (NCL) are a subset of lysosomal storage diseases 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 are typically inherited in an autosomal recessive manner, although one adult onset form (ANCL; *DNAJC5* gene) has been shown to be autosomal dominant.

First-tier biochemical testing is available for the 2 most common types of enzyme deficiency resulting in NCL: TPPTL / Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Leukocytes.

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.

Glycogen Storage Disease Panel

Glycogen storage diseases (GSD) are a group of inherited metabolic conditions caused by deficiency of enzymes responsible for glycogen metabolism, resulting in abnormal storage of glycogen in the liver and various muscles. There are over 15 different GSD, which vary in symptoms and severity depending on the enzyme deficiency, with liver and muscle tissues most commonly affected.

Generally they can be divided into 2 categories, those with hepatic involvement and those with neuromuscular involvement. Some GSD result in single tissue disease, while others affect multiple organs. Clinical features may include hepatomegaly, hypoglycemia, muscle cramps, exercise intolerance, and progressive fatigue and weakness. Preliminary biochemical testing may be helpful in making a diagnosis. Recommended first-tier biochemical testing includes glucose monitoring, triglycerides, uric acid level, creatine kinase, liver function tests, and complete blood count.

Peroxisomal Disorder Panel

Peroxisomes are responsible for catabolic actions of cells, including beta oxidation of very long chain fatty acids, and anabolic actions, including biosynthesis of bile acids and plasmalogens. Peroxisomal disorders can be categorized into 2 major groups based on the function that is disrupted: peroxisomal biogenesis disorders and single peroxisomal enzyme deficiencies.

Peroxisomal biogenesis disorders are caused by defective assembly of the organelle resulting in some amount of deficient functional peroxisomes. Severity of disease is dependent on the amount of remaining functional peroxisomes. Peroxisomal biogenesis disorders include those in the Zellweger spectrum: Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Clinical features include developmental delay, liver disease, blindness, and deafness, and are usually progressive. Severity is variable with Zellweger syndrome being most severe and infantile Refsum disease being least severe. These diseases are due to mutations in the *PEX* genes that are responsible for encoding proteins for peroxisome assembly.

Peroxisomal enzyme deficiencies cause a disruption in peroxisomal function, although the organelles remain intact.

The most common peroxisomal disorder, X-linked adrenoleukodystrophy, is an enzyme deficiency due to mutations in the *ABCD1* gene. Other enzyme deficiencies include rhizomelic chondrodysplasia type 2 and 3, and congenital bile acid synthesis defect.

Preliminary biochemical testing may be helpful in making a diagnosis. Recommended first-tier biochemical testing analyzes very long chain fatty acids. Refer to POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum for more information.

Custom Gene Panel

Custom gene ordering allows the creation of a custom gene list to tailor testing to a patient's exact need. After selection of a specific disease state, the custom gene panel can be modified to add or remove genes. Through this option single gene testing can be performed.

Reference Values

An interpretive report will be provided.

Interpretation

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

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 predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a mutation that is not identified by the methods performed (eg, promoter mutations or deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of disease.

For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene mutation in an affected family member.

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

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified. Due to the limitations of next-generation sequencing, small deletions and insertions may not be detected by this test. If a diagnosis of one of the syndromes on this panel is still suspected, consider full gene sequencing using traditional Sanger methods.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated

regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently not validated.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

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. At this time, it is not standard practice for the laboratory to systematically review likely deleterious alterations or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

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 May;17(5):405-424

2. Wang RY, Bodamer OA, Watson MS, et al: 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. Human 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 Feb;117(2):53-65

6. Robak LA, Jansen IE, van Rooij et al: Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. Brain 2017 Dec; 140 (12): 3191-3203

7. Waterham, HR, Ebberink MS: Genetics and molecular basis of human peroxisome biogenesis disorders. Biochim Biophys Acta 2012;1822(9):1430-1441

8. Wanders RJ: Metabolic and molecular basis of peroxisomal disorders: a review. Am J Med Genet A 2004;126A(4):355-375

9. Wanders RJ, Waterham HR: Peroxisomal disorders: the single peroxisomal enzyme deficiencies. Biochim Biophys Acta 2006;1763(12):1707-1720

10. Fidaleo M: Peroxisomes and peroxisomal disorders: the main facts. Exp Toxicol Pathol 2010;62(6):615-625

11. Chen YT, Kishani PS, Koeberl D: Glycogen Storage Disease. The Online Metabolic and Molecular Bases of Inherited Diseases. Edited by D Valle, B Vogelstein, KW Kinzler, et al. Accessed on: December 12, 2018

12. Hicks J, Wartchow, E, Mierau G: Glycogen Storage Diseases: A Brief Review and Update on Clinical Features,

Genetic Abnormalities, Pathologic Features, and Treatmen. Ultrastruct Pathol 2011;35(5):183-196

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of a mutation in the genes analyzed. Additionally, NGS is used to test for the presence of large deletions and/or duplications in all genes on the panel listed above. PCR, qPCR, and/or Sanger sequencing is used to confirm alterations detected by NGS when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

4 weeks

Maximum Laboratory Time

5 weeks

Specimen Retention Time

Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81403 (if appropriate)

81404 (if appropriate)

81405 (if appropriate)

81406 (if appropriate)

81407 (if appropriate)

81479 (if appropriate)

81443 (if appropriate)

88233 (if appropriate)

88240 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
LPGD	Lysosome, Peroxisome, GSD Panels	In Process

Result ID	Test Result Name	Result LOINC Value
MG122	Client Provided Sub-Panel	19145-2
MG123	Gene List ID or NA	48018-6
605165	Result Summary	In Process
605166	Result	82939-0
605167	Interpretation	69047-9
605168	Additional Information	48767-8
605169	Method	49549-9
605170	Disclaimer	62364-5
605171	Specimen	31208-2
605172	Source	31208-2
605173	Released By	18771-6