Overview

Useful For
Follow up for abnormal biochemical results suggestive of a methylmalonic acidemia

Establishing a molecular diagnosis for patients with methylmalonic acidemia

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

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 25 genes associated with methylmalonic aciduria: ABCD4, ACSF3, ALDH6A1, AMN, CD320, CUBN, CBLIF, HCFC1, LMBRD1, MCEE, MMAA, MMAB, MMACHC, MMADHC, MTHFR, MTR, MTRR, MMUT, PRDX1, SUCLA2, SUCLG1, TCN1, TCN2, THAP11, ZNF143. See Targeted Genes and Methodology Details for Methylmalonic Aciduria Gene Panel in Special Instructions and Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for methylmalonic aciduria.

Additional first tier testing may be considered/recommended.

For more information see Ordering Guidance.

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Methylmalonic Aciduria Gene Panel

Method Name

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

NY State Available

No

Specimen

Specimen Type

Varies

Ordering Guidance

The recommended first-tier tests to screen for methylmalonic aciduria include plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Urine), and homocysteine (HCYSP / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum).

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. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**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

**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**

See Specimen Required

**Reject Due To**

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

**Specimen Stability Information**

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**Clinical and Interpretive**

**Clinical Information**

Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism.
MMA is a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase caused by pathogenic variants in the mutase gene (MUT). Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin (Cbl) synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin.

Since the first reports of this disorder in 1967, hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels (MMAP / Methylmalonic Acid, Quantitative, Plasma and MMAU / Methylmalonic Acid, Quantitative, Urine).

Plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Urine), and homocysteine (HCYS / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum) are recommended first-tier biochemical tests to screen patients for methylmalonic acidemia.

A comprehensive gene panel is a helpful tool to establish a targeted diagnosis for patients with suggestive clinical and biochemical features of methylmalonic acidemia.

Treatment is most effective when tailored to the specific type of methylmalonic acidemia. For example, intramuscular injections of hydrocobalamin are critical in the treatment of Cbl C, whereas oral cyanocobalamin is effective for methylmalonic acidemia mutase subtypes as well as other cobalamin subtypes. Acute treatment for methylmalonic acidemia consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been successful in treating some patients.

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.

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 a reportable variant in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options, for assistance in general test selection, or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted 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, but 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 specific clinical disorders are suspected, evaluation by alternative methods can be considered.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, these 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.

There may be regions of genes that cannot be effectively amplified for 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 assay will not reliably detect insertions/deletions (indels) of 40 or more base pairs (bp), including Alu insertions, long interspersed nuclear elements (LINES), and short interspersed nuclear elements (SINES). The bioinformatics software pipeline is verified to detect 95% of deletions up to 75 bp and insertions up to 47 bp.

Additionally, low level mosaic variants may not be detected.

This test is not designed 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.

Reclassification of Variants-Policy:

At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. 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.

Variant Evaluation:

Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) recommendations as a guideline. 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. Intronic and synonymous sequence variants not predicted to impact splicing or otherwise contribute to disease are not reported.

Clinical Reference


Test Definition: MMAGP
Methylmalonic Aciduria Gene Panel

http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086103

Performance

Method Description

Next generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed. NGS and/or a polymerase chain reaction (PCR)-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 amplified for 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 may be performed by alternate methodologies based on internal laboratory criteria.

PCR-based methods and/or Sanger sequencing is used to confirm variants detected by NGS when appropriate. (Unpublished Mayo method)

See Targeted Genes for Methodology Details for Methylmalonic Aciduria Gene Panel in Special Instructions for details regarding the targeted gene regions for this test.

Genes analyzed:

ABCD4, ACSF3, ALDH6A1, AMN, CD320, CUBN, CBLIF, HCFC1, LMBRD1, MCEE, MMAA, MMAB, MMACHC, MMADHC, MTHFR, MTR, MTRR, MMUT, PRDX1, SUCLA2, SUCLG1, TCN1, TCN2, THAP11, ZNF143

PDF Report

No

Day(s) Performed

Varies

Report Available

3 to 4 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 US Food and Drug Administration.
## Test Definition: MMAGP

*Methylmalonic Aciduria Gene Panel*

### CPT Code Information

81443

### LOINC® Information

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