Overview

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

Establishing a molecular diagnosis for patients with methylmalonic acidemia or propionic acidemia

Identifying variants within genes known to be associated with methylmalonic acidemia or propionic 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 28 genes associated with methylmalonic aciduria-propionic aciduria: ABCD4, ACSF3, ALDH6A1, AMN, CD320, CUBN, DMGDH, CBLIF, HCFC1, LMBRD1, MCEE, MMAA, MMAB, MMACHC, MMADHC, MTHFR, MTR, MTRR, MMUT, PCCA, PCCB, PRDX1, SUCLA2, SUCLG1, TCN1, TCN2, THAP11, ZNF143. See Targeted Genes and Methodology Details for Methylmalonic Aciduria-Propionic Aciduria Combined 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 and propionic 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-Propionic Aciduria Combined Gene Panel

Method Name
Custom 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
Additional recommended first-tier tests to screen for methylmalonic acidemia 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

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are defects of propionate metabolism caused by deficiencies in methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMA includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal methylmalonic acid concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. All known disorders of MMA and PA metabolism are inherited in an autosomal recessive manner.

Newborn screening for inborn errors of propionic acid metabolism relies on elevations of methionine and propionyl carnitine, which are reported as an elevation of C3. These analytes are not specific for this condition and are prone to false-positive results, leading to increased cost, stress, and anxiety for families who are subjected to follow-up testing. Homocysteine, methylmalonic acid, and methylcitric acid are more specific markers for inborn errors of propionic acid metabolism (HCMM / Homocysteine (Total), Methylmalonic Acid, and Methylcitric Acid, Blood Spot).

For MMA, the preferred biochemical screening tests 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 (HCYS / Homocysteine, Total, Plasma or HCY / Homocysteine, Total, Serum).

Molecular genetic testing can be used to confirm a biochemical diagnosis for MMA or PA.

Treatment is most effective when tailored to the specific type of MMA or PA. For example, intramuscular injections of hydrocobalamin are critical in the treatment of Cbl C, whereas oral cyanocobalamin is effective for MMA mutase subtypes as well as other cobalamin subtypes. Acute treatment for MMA and PA is similar, consisting 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 used with success in treating some patients with MMA or PA.

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.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. Intronic and synonymous sequence variants not predicted to impact splicing or otherwise contribute to disease are not reported.

Clinical Reference


Test Definition: MPAGP
MMA PA Combined Gene Panel

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 and Methodology Details for Methylmalonic Aciduria-Propionic Aciduria Combined Gene Panel in Special Instructions for details regarding the targeted gene regions for this test.

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

PDF Report
No

Day(s) Performed
Varies

Report Available
3 to 4 weeks

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.

CPT Code Information
81443

LOINC® Information
## Test Definition: MPAGP

**MMA PA Combined Gene Panel**

### Test ID

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