Overview

Useful For

Confirmation of diagnosis of disorders belonging to the cblD complementation group

Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified

Distinguishing between cblA, cblB, and cblD variant 2 when methylmalonic aciduria is identified

Distinguishing between cblD variant 1, cblE, and cblG when homocystinuria is identified

Carrier screening in cases where there is a family history of methylmalonic aciduria or homocystinuria, but disease-causing mutations have not been identified in an affected individual

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Testing Algorithm

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

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)
- Blood Spot Collection Instructions

Method Name

Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

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.

Submit only 1 of the following specimens:

Preferred:

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/Frozen

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

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 [T115]).

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

Specimen Type: Blood spot

Supplies: Card - Blood Spot Collection (Filter Paper) (T493)

Container/Tube:

Preferred: Collection card (Whatman Protein Saver 903 Paper)

Acceptable: Ahlstrom 226 filter paper, or Blood Spot Collection Card (T493)

Specimen Volume: 2 to 5 Blood Spots on collection card (Whatman Protein Saver 903 Paper; Ahlstrom 226 filter paper; or Blood Spot Collection Card, T493)

Collection Instructions:

1. An alternative blood collection option for a patient >1 year of age is finger stick.

2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 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. For collection instructions, see Blood Spot Collection Instructions in Special Instructions.

2. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777) in Special Instructions.

3. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800) in Special Instructions.

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

3. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-Benign Hematology Test Request Form (T755)

-Inborn Errors of Metabolism Test Request (T798)

Specimen Minimum Volume

Blood: 1 mL
Blood Spots: 5 punches, 3-mm diameter

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

Several causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 8 distinct complementation classes (cblA-cblH). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both.

cblD type is a rare autosomal recessive disorder with variable clinical presentations. It can present as cblD variant 1, associated with isolated homocystinuria; cblD variant 2, associated with isolated methylmalonic aciduria; or as cblD combined, associated with both methylmalonic aciduria and homocystinuria. cblD variant 1 is associated with clinical features of isolated homocystinuria, including megaloblastic anemia and neurological abnormalities, as well as developmental delays. cblD variant 2 is associated with clinical features of isolated methylmalonic aciduria, including metabolic decomposition, which can result in lethargy, failure to thrive, feeding problems, and hypotonia. cblD combined is associated with clinical features of both methylmalonic aciduria and homocystinuria. Biochemical presentation includes methylmalonic aciduria and/or homocystinuria in urine organic acid or plasma amino acid analysis.(1) Other complementation class disorders can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types.

Mutations in the *MMADHC* gene are responsible for the cblD type disorder. To date, 9 mutations in 7 individuals have been identified.(2) Three missense mutations identified in exons 6 and 8 have been associated with cblD variant 1. One nonsense mutation, 1 in-frame duplication, and 1 frame-shift deletion in exons 3 and 4 have been associated with cblD variant 2. One nonsense mutation, 1 frame-shift duplication, and 1 splice-site deletion in exons 5 and 8 and intron 7 have been associated with cblD combined.

Reference Values

An interpretive report will be provided.

Interpretation

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

Cautions

A small percentage of individuals who are carriers or have a diagnosis of methylmalonic aciduria and homocystinuria, cblD type (MMADHC) may have a mutation that is not identified by this method (eg, large genomic deletions, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of MMADHC. For carrier testing, it is important to first document the presence of a *MMADHC* gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

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.

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

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. Suormala T, Baumgartner MR, Coelho D, et al: The cblD Defect Causes Either Isolated or Combined Deficiency of Methylcobalamin and Adenosylcobalamin Synthesis. J Biol Chem 2004;279(41):42742-42749

3. Coelho D, Suormala T, Stucki M, et al: Gene Identification for the cblD Defect of Vitamin B12 Metabolism. N Engl J Med 2008;358:1454-1464

4. Goodman SI, Moe PG, Hammond KB, et al: Homocystinuria with methylmalonic aciduria: two cases in a sibship. Biochem Med 1970;4(5):500-515

5. Cooper BA, Rosenblatt DS, Watkins D: Methylmalonic Aciduria Due to a New Defect in Adenosylcobalamin Accumulation by Cells. Am J Hematol 1990;34:115-120

Performance

Method Description

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *MMADHC* gene.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly; Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

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

81479-Unlisted molecular pathology procedure

Fibroblast Culture for Genetic Test

88233-Tissue culture, skin or solid tissue biopsy (if appropriate)

88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
MHDZ	MMADHC Gene, Full Gene Analysis	94207-8

Result ID	Test Result Name	Result LOINC Value
53992	Result Summary	50397-9
53993	Result	82939-0
53994	Interpretation	69047-9
53995	Additional Information	48767-8
53996	Specimen	31208-2
53997	Source	31208-2
53998	Released By	18771-6