

## Overview

### Useful For

Confirmation of diagnosis of disorders belonging to the cbID complementation group

Distinguishing between cbIC, cbID, and cbIF types when methylmalonic aciduria and homocystinuria are identified

Distinguishing between cbIA, cbIB, and cbID variant 2 when methylmalonic aciduria is identified

Distinguishing between cbID variant 1, cbIE, and cbIG 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 \(Spanish\)](#)

### 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.

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**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)

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**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 in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777) in Special Instructions.
2. 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.

cbID type is a rare autosomal recessive disorder with variable clinical presentations. It can present as cbID variant 1, associated with isolated homocystinuria; cbID variant 2, associated with isolated methylmalonic aciduria; or as cbID combined, associated with both methylmalonic aciduria and homocystinuria. cbID variant 1 is associated with clinical features of isolated homocystinuria, including megaloblastic anemia and neurological abnormalities, as well as developmental delays. cbID 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. cbID 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 cbID 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 cbID variant 1. One nonsense mutation, 1 in-frame duplication, and 1 frame-shift deletion in exons 3 and 4 have been associated with cbID 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 cbID 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, cbID 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 cbID 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 cbID 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