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## Overview

### Useful For

[Second-tier assay of newborn screening specimens when abnormal propionyl carnitine](#) or methionine concentrations are identified in a primary newborn screen

### Special Instructions

- [Biochemical Genetics Patient Information](#)
- [Blood Spot Collection Card-Spanish Instructions](#)
- [Blood Spot Collection Card-Chinese Instructions](#)
- [Blood Spot Collection Instructions](#)

### Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

### NY State Available

Yes

## Specimen

### Specimen Type

Whole blood

### Ordering Guidance

The preferred test for evaluating adults for an inherited disorder of methionine, cobalamin, or propionate metabolism is CMMPP / Cobalamin, Methionine, and Methylmalonic Acid Pathways, Plasma or CMMPS / Cobalamin, Methionine, and Methylmalonic Acid Pathways, Serum.

### Specimen Required

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

### Container/Tube:

**Preferred:** Card-Blood Spot Collection (Filter Paper)

**Acceptable:** Local newborn screening card, Whatman Protein Saver 903 filter paper, PerkinElmer 226 (formerly Ahlstrom 226) filter paper, Munktell filter paper

**Specimen Volume:** 2 Blood spots

### Collection Instructions:

1. **Do not use** device or capillary tube containing EDTA or ACD to collect specimen. Sodium heparin is acceptable but must be spotted on card the same day as collected.
2. Completely fill at least 2 circles on the filter paper card (approximately 100 microliters blood per circle) using blood from a heel or finger stick.
3. Let blood dry on filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
4. Do not expose specimen to heat or direct sunlight.
5. Do not stack wet specimens.
6. Keep specimen dry.

**Additional Information:**

1. For collection instructions, see [Blood Spot Collection Instructions](#)
2. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777)
3. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800)

**Forms**

1. [Biochemical Genetics Patient Information](#) (T602)
2. [If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request](#) (T798) with the specimen.

**Reject Due To**

Shows serum rings; Insufficient specimen    Reject

**Specimen Minimum Volume**

1 Blood spot

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Whole blood	Ambient (preferred)		FILTER PAPER
	Frozen		FILTER PAPER
	Refrigerated		FILTER PAPER

**Clinical & Interpretive**

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**Clinical Information**

Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, mental retardation, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine (free and total) along with decreased concentrations of cystine.

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.

Newborn screening for inborn errors of methionine and propionic acid metabolism relies on elevations of methionine and propionyl carnitine. These analytes are not specific for these conditions 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 methionine and propionic acid metabolism. Molecular genetic testing can be used to confirm a biochemical diagnosis for homocystinuria, methylmalonic acidemia, and propionic acidemia.

**Reference Values**

HOMOCYSTEINE:

&lt;9.0 nmol/mL

METHYLMALONIC ACID:

&lt;4.0 nmol/mL

METHYLCITRIC ACID:

&lt;1.0 nmol/mL

An interpretive report will also be provided.

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**Interpretation**

Elevated homocysteine, methylcitric acid, or methylmalonic acid concentrations are indicative of an underlying metabolic disorder.

**Cautions**

Normal levels may be seen in affected individuals undergoing treatment.

**Supportive Data**

In a Mayo study that analyzed specimens from 200 unaffected neonates, clear clinical discrimination was observed when compared to patients with defects of propionate or methionine metabolism. The 99.5 percentile, determined from the analysis of 200 dried blood spots of unaffected controls, for methylmalonic acid (MMA), methylcitric acid (MCA), and homocysteine (HCY), are 1.58 nmol/mL, 0.62 nmol/mL, and 9.9 nmol/mL, respectively, providing clear clinical discrimination from patients with defects of propionate or methionine metabolism (eg, methylmalonic acidemia: MMA=31.9 nmol/mL; propionic acidemia: MCA=12.8 nmol/mL; homocystinuria: HCY=189 nmol/mL).

**Clinical Reference**

1. Pasquali M, Longo N: Newborn screening and inborn errors of metabolism. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1697-1730
2. Tortorelli S, Turgeon CT, Lim JS, et al: Two-tier approach to the newborn screening of methylenetetrahydrofolate reductase deficiency and other remethylation disorders with tandem mass spectrometry. *J Pediatr.* 2010 Aug;157(2):271-275
3. Harvey Mudd S, Levy HL, Kraus JP: Disorders of transsulfuration. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 17, 2020. Available at <https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225084718>

**Performance****Method Description**

Total homocysteine, 2-methylcitric acid, and methylmalonic acid are measured by stable isotope dilution microflow liquid chromatography tandem mass spectrometry. (Turgeon CT, Magera MJ, Cuthbert CD, et al: Determination of total homocysteine, methylmalonic acid, and 2-methylcitric acid in dried blood spots by tandem mass spectrometry. *Clin Chem.* 2010 Nov; 56[11]:1686-1695)

**PDF Report**

No

**Specimen Retention Time**

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1 year

**Performing Laboratory Location**

Rochester

**Fees & Codes****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**

83090

83918

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
HCMM	HCMM, BS	In Process

Result ID	Reporting Name	LOINC®
50252	Homocysteine	54301-7
50253	Methylmalonic Acid	82385-6
50254	Methylcitric Acid	82386-4
50257	Reviewed By	18771-6
50255	Interpretation	59462-2