MAYO CLINIC LABORATORIES

Test Definition: HCMM

Homocysteine (Total), Methylmalonic Acid, and Methylcitric Acid, Blood Spot

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: Blood Spot Collection Card (Filter Paper)
Acceptable: Local newborn screening card, Whatman Protein Saver 903 filter paper, PerkinElmer 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.

Specimen Minimum Volume

1 Blood spot

Reject Due To

Shows serum rings Insufficient specimen	Reject

Specimen Stability Information

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

Clinical & Interpretive

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, intellectual disability, 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:
<9.0 nmol/mL

Methylmalonic Acid:
<4.0 nmol/mL

Methylcitric Acid:
<1.0 nmol/mL

An interpretive report will also be provided.

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;157(2):271-275
3. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Valle DL,

Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed October 07, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086103
4. 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 October 7, 2024. 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 stabile 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;56[11]:1686-1695)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
2 to 4 days

Specimen Retention Time
1 year

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

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CPT Code Information

83090
83918

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
HCMM	HCMM, BS	100765-7

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