MAYO CLINIC LABORATORIES

Test Definition: CMMPP

Cobalamin, Methionine, and Methylmalonic Acid Pathways, Plasma

Overview

Useful For

Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine, cobalamin, or propionate metabolism using plasma specimens

Evaluating individuals with suspected deficiency of vitamin B12

Special Instructions

- Biochemical Genetics Patient Information

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Plasma

Necessary Information

Patient's age and sex are required.

Specimen Required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Green top (sodium or lithium heparin)
Submission Container/Tube: Plastic vial
Specimen Volume: 1 mL
Collection Instructions:
1. Immediately place specimen on ice.
2. Within 4 hours of collection, centrifuge and aliquot plasma into plastic vial. **Note:** If blood cannot be placed on wet ice immediately, centrifuge and aliquot plasma into a plastic vial within 1 hour of collection.
3. A refrigerated centrifuge is not required if the above time restrictions are met.

Forms

1. Biochemical Genetics Patient Information (T602)

2. If not ordering electronically, complete, print, and send 1 of the following with the specimen:
-Biochemical Genetics Test Request (T798)
-Benign Hematology Test Request Form (T755)

Specimen Minimum Volume
0.4 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Plasma	Refrigerated (preferred)	28 days	
	Ambient	28 days	
	Frozen	309 days	

Clinical & Interpretive

Clinical Information
Homocysteine, methylmalonic acid (MMA), methylcitric acid, methionine, cysteine, and cystathionine can be used to evaluate patients for inborn errors of methionine, cobalamin, and propionate metabolism. Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle.

Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation.

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, developmental delay, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine along with decreased concentrations of cystine.

Elevated levels of MMA result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12.

Enzymatic deficiencies of propionyl-CoA carboxylase and methylmalonyl-CoA mutase are associated with propionic academia (PA) and methylmalonic acidemia mut(0/-) type (MMAmut), respectively. The clinical phenotype includes

vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMAmut includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal MMA concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase.

Inherited conditions of cobalamin (Cbl) absorption and transport are caused by variants in several genes encoding Cbl binding factors and transmembrane transporters and receptors. In addition, inside the cell, Cbl undergoes several steps of modification until it reaches a divergent point beyond which 2 separate paths lead to the formation of the 2 active components of this cofactor: adenosylcobalamin (AdoCbl), a cofactor for methylmalonyl-CoA mutase; and methylcobalamin (MeCbl), a cofactor for methionine synthase, remethylating homocysteine to methionine.

Defects of AdoCbl and MeCbl metabolism after the point where the synthetic pathways separate lead to isolated deficiencies of methylmalonyl-CoA mutase (elevations of propionyl carnitine, MMA, and methylcitric acid) or methionine synthase (elevated homocysteine with low/low normal methionine) respectively. Defects prior to this point are associated with deficiencies of both enzymes and lead to elevation of all markers (propionyl carnitine, MMA, methylcitric acid, and homocysteine).

Acquired cobalamin (vitamin B12) deficiency can be a result of pernicious anemia, vegan diet, malabsorption, and decreased intrinsic factor excretion (secondary to gastrectomy) and can be distinguished from most inherited defects (particularly intracellular deficiencies) with the identification of decreased levels of vitamin B12. Older adult patients with acquired cobalamin deficiency may present with megaloblastic anemia, peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. Additional testing with homocysteine and MMA determinations may help distinguish between vitamin B12 and folate deficiency states.

Reference Values

Age	Total homocysteine (nmol/mL)		Methylmalonic acid (nmol/mL)	2-Methylcitric acid (nmol/mL)	Total cysteine (nmol/mL)	Methionine (nmol/mL)		Cys (nm
	Female	Male				Female	Male	
0-11 months	3.1-8.3	3.2-9.7	0.08-0.32	0.02-0.35	142.8-258.8	14.7-43.1	14.5-42.3	0.07
12-23 months	3.2-8.3	3.3-9.6	0.08-0.31	0.02-0.35	143.7-258.7	14.7-43.1	14.5-42.2	0.07
24-35 months	3.2-8.2	3.3-9.6	0.08-0.31	0.02-0.35	144.8-258.6	14.7-43.0	14.5-42.1	0.07
3 years	3.2-8.2	3.3-9.6	0.08-0.31	0.02-0.35	146.0-258.5	14.7-43.0	14.5-42.0	0.07
4 years	3.3-8.2	3.4-9.5	0.08-0.30	0.02-0.35	148.2-258.4	14.7-42.8	14.5-41.8	0.07
5 years	3.4-8.1	3.5-9.4	0.08-0.30	0.02-0.35	150.6-258.3	14.8-42.7	14.5-41.6	0.07
6 years	3.5-8.1	3.6-9.4	0.08-0.29	0.02-0.35	153.2-258.3	14.8-42.5	14.5-41.4	0.07
7 years	3.5-8.1	3.7-9.4	0.08-0.29	0.02-0.35	155.8-258.4	14.8-42.2	14.5-41.1	0.07
8 years	3.6-8.2	3.8-9.3	0.08-0.28	0.02-0.35	158.5-258.7	14.9-42.0	14.6-40.9	0.07
9 years	3.7-8.2	3.9-9.4	0.09-0.28	0.02-0.35	161.0-259.1	14.9-41.7	14.6-40.7	0.07
10 years	3.8-8.3	4.1-9.4	0.09-0.28	0.02-0.35	163.5-259.7	15.0-41.4	14.7-40.6	0.07
11 years	3.9-8.4	4.3-9.4	0.09-0.28	0.02-0.35	165.9-260.5	15.1-41.0	14.8-40.4	0.07

12 years	3.9-8.6	4.4-9.5	0.09-0.27	0.02-0.35	168.4-261.4	15.1-40.7	14.9-40.3	0.07
13 years	4.0-8.7	4.6-9.6	0.09-0.27	0.02-0.35	170.9-262.4	15.2-40.3	15.1-40.1	0.07
14 years	4.1-8.8	4.8-9.7	0.09-0.27	0.02-0.35	173.6-263.6	15.3-39.9	15.3-40.0	0.07
15 years	4.2-8.9	5.0-9.8	0.09-0.27	0.02-0.35	176.4-264.7	15.4-39.5	15.5-39.9	0.07
16 years	4.2-9.1	5.2-9.9	0.09-0.27	0.02-0.35	179.3-265.9	15.5-39.1	15.8-39.7	0.07
17 years	4.3-9.2	5.4-10.0	0.09-0.27	0.02-0.35	182.2-267.1	15.6-38.7	16.1-39.6	0.07
18 years	4.3-9.3	5.6-10.1	0.08-0.27	0.02-0.35	184.9-268.3	15.7-38.2	16.4-39.4	0.07
19 years	4.4-9.5	5.7-10.3	0.08-0.26	0.02-0.35	187.4-269.4	15.7-37.8	16.7-39.3	0.07
20 years	4.4-9.6	5.9-10.5	0.08-0.26	0.02-0.35	189.5-270.5	15.8-37.3	17.0-39.1	0.07
21 years	4.4-9.8	6.0-10.6	0.08-0.26	0.02-0.35	191.2-271.7	15.9-36.8	17.3-38.9	0.07
22 years	4.4-9.9	6.1-10.8	0.08-0.27	0.02-0.35	192.5-272.8	15.9-36.3	17.6-38.7	0.07
23 years	4.4-10.1	6.2-11.0	0.08-0.27	0.02-0.35	193.5-274.1	15.9-35.8	17.9-38.5	0.07
24 years	4.4-10.3	6.2-11.1	0.08-0.27	0.02-0.35	194.2-275.4	15.9-35.3	18.1-38.3	0.07
25 years	4.4-10.4	6.3-11.3	0.08-0.28	0.02-0.35	194.8-277.0	15.9-34.8	18.2-38.1	0.07
26 years	4.4-10.6	6.3-11.4	0.08-0.28	0.02-0.35	195.3-278.6	15.9-34.3	18.4-37.9	0.07
27 years	4.3-10.8	6.4-11.6	0.08-0.28	0.02-0.35	196.0-280.5	16.0-33.8	18.5-37.7	0.07
28 years	4.3-11.0	6.4-11.7	0.08-0.29	0.02-0.35	196.7-282.4	16.0-33.4	18.7-37.5	0.07
29 years	4.3-11.2	6.4-11.8	0.08-0.29	0.02-0.35	197.7-284.3	16.0-33.0	18.8-37.3	0.07
30 years	4.3-11.4	6.4-11.9	0.08-0.30	0.02-0.35	198.8-286.3	16.1- 32.6	18.9-37.1	0.07
31 years	4.4-11.6	6.4-12.1	0.08-0.30	0.02-0.35	200.2-288.2	16.1-32.2	19.0-36.9	0.07
32 years	4.4-11.8	6.4-12.2	0.08-0.31	0.02-0.35	201.7-290.0	16.1-31.8	19.1-36.7	0.07
33 years	4.4-11.9	6.4-12.3	0.08-0.31	0.02-0.35	203.4-291.5	16.1-31.5	19.2-36.5	0.07
34 years	4.5-12.1	6.4-12.4	0.08-0.31	0.02-0.35	205.2-292.9	16.1-31.2	19.3-36.3	0.07
35 years	4.5-12.2	6.4-12.6	0.08-0.32	0.02-0.35	207.2-294.1	16.1-30.8	19.4-36.1	0.07
36 years	4.6-12.4	6.4-12.8	0.08-0.32	0.02-0.35	209.3-295.1	16.1-30.5	19.5-35.9	0.07
37 years	4.6-12.5	6.4-12.9	0.08-0.33	0.02-0.35	211.5-296.0	16.1-30.2	19.6-35.6	0.07
38 years	4.7-12.7	6.4-13.1	0.08-0.33	0.02-0.35	213.8-296.9	16.1-29.9	19.7-35.4	0.07
39 years	4.7-12.8	6.4-13.2	0.08-0.34	0.02-0.35	216.3-297.7	16.1-29.7	19.8-35.2	0.07
40 years	4.8-13.0	6.5-13.4	0.08-0.34	0.02-0.35	218.9-298.7	16.1-29.4	19.9-35.0	0.07
41 years	4.8-13.2	6.5-13.5	0.08-0.35	0.02-0.35	221.6-299.7	16.1-29.2	20.0-34.8	0.07
42 years	4.8-13.4	6.5-13.7	0.08-0.36	0.02-0.35	224.3-300.8	16.2-29.0	20.1-34.6	0.07
43 years	4.9-13.5	6.6-13.9	0.08-0.36	0.02-0.35	227.0-302.0	16.2-28.8	20.2-34.4	0.07
44 years	4.9-13.7	6.6-14.0	0.08-0.37	0.02-0.35	229.8-303.5	16.3-28.6	20.3-34.2	0.07
45 years	4.9-13.9	6.6-14.2	0.08-0.38	0.02-0.35	232.6-305.2	16.3-28.5	20.3-34.0	0.07
46 years	4.9-14.0	6.7-14.4	0.08-0.38	0.02-0.35	235.3-307.3	16.4-28.4	20.4-33.8	0.07
47 years	4.9-14.2	6.7-14.5	0.08-0.39	0.02-0.35	238.0-309.7	16.4-28.2	20.4-33.6	0.07
48 years	5.0-14.3	6.8-14.7	0.08-0.39	0.02-0.35	240.8-312.6	16.5-28.1	20.5-33.3	0.07
49 years	5.0-14.4	6.8-14.9	0.08-0.40	0.02-0.35	243.5-315.9	16.5-28.0	20.5-33.1	0.07
50 years	5.0-14.5	6.8-15.0	0.08-0.40	0.02-0.35	246.2-319.7	16.5-27.9	20.6-32.8	0.07
51 years	5.1-14.6	6.8-15.2	0.08-0.41	0.02-0.35	248.9-323.8	16.5-27.8	20.6-32.5	0.07
52 years	5.1-14.7	6.9-15.4	0.08-0.41	0.02-0.35	251.5-328.1	16.5-27.6	20.7-32.3	0.07
53 years	5.1-14.8	6.9-15.5	0.08-0.42	0.02-0.35	254.0-332.4	16.5-27.5	20.8-32.1	0.07
54 years	5.2-14.9	6.9-15.6	0.08-0.42	0.02-0.35	256.4-336.5	16.5-27.4	21.0-31.9	0.07

55 years	5.2-15.0	6.9-15.7	0.08-0.43	0.02-0.35	258.6-340.2	16.5-27.3	21.1-31.7	0.07
56 years	5.3-15.0	6.9-15.8	0.08-0.43	0.02-0.35	260.6-343.6	16.6-27.2	21.2-31.5	0.07
57 years	5.3-15.1	6.9-15.9	0.08-0.44	0.02-0.35	262.5-346.5	16.6-27.1	21.2-31.3	0.07
58 years	5.3-15.2	6.9-16.0	0.08-0.44	0.02-0.35	264.3-349.0	16.6-27.1	21.3-31.0	0.07
59 years	5.4-15.2	6.9-16.0	0.08-0.44	0.02-0.35	266.2-351.1	16.7-27.1	21.3-30.8	0.07
60 years	5.4-15.3	6.9-16.1	0.08-0.45	0.02-0.35	268.3-353.1	16.8-27.1	21.3-30.6	0.07
61 years	5.4-15.4	7.0-16.2	0.09-0.45	0.02-0.35	270.8-355.1	16.9-27.2	21.3-30.3	0.07
62 years	5.5-15.4	7.0-16.2	0.09-0.46	0.02-0.35	273.8-357.3	17.0-27.2	21.2-30.0	0.08
63 years	5.5-15.5	7.0-16.3	0.09-0.46	0.02-0.35	277.5-359.7	17.1-27.3	21.2-29.8	0.08
64 years	5.6-15.5	7.1-16.3	0.09-0.46	0.02-0.35	281.9-362.3	17.2-27.4	21.1-29.5	0.08
65 years	5.6-15.6	7.1-16.3	0.09-0.47	0.02-0.35	286.9-365.2	17.3-27.6	21.1-29.2	0.08
66 years	5.7-15.6	7.1-16.3	0.09-0.47	0.02-0.35	292.4-368.3	17.4-27.7	21.1-29.0	0.08
67 years	5.7-15.7	7.2-16.3	0.09-0.47	0.02-0.35	298.1-371.6	17.5-27.8	21.0-28.7	0.09
68 years	5.8-15.7	7.2-16.3	0.09-0.47	0.02-0.35	303.6-374.8	17.7-27.9	21.0-28.5	0.09
69 years	5.9-15.7	7.2-16.3	0.09-0.47	0.02-0.35	308.7-377.8	17.8-28.0	21.0-28.4	0.09
70 years	6.0-15.8	7.3-16.3	0.09-0.48	0.02-0.35	313.1-380.7	18.0-28.1	21.0-28.3	0.09
71 years	6.1-15.8	7.3-16.3	0.09-0.48	0.02-0.35	316.5-383.2	18.1-28.2	20.9-28.2	0.09
72 years	6.2-15.8	7.3-16.3	0.09-0.48	0.02-0.35	318.9-385.3	18.3-28.3	20.9-28.0	0.09
73 years	6.3-15.9	7.3-16.3	0.09-0.48	0.02-0.35	320.1-387.0	18.5-28.4	20.8-27.9	0.10
74 years	6.4-15.9	7.3-16.3	0.09-0.48	0.02-0.35	320.6-388.3	18.8-28.5	20.8-27.8	0.10
75 years	6.5-15.9	7.3-16.3	0.09-0.48	0.02-0.35	320.3-389.3	19.1-28.5	20.8-27.7	0.10
76 years	6.6-15.9	7.3-16.3	0.09-0.48	0.02-0.35	319.6-389.9	19.3-28.6	20.8-27.5	0.10
77 years	6.7-16.0	7.4-16.3	0.10-0.48	0.02-0.35	319.1-390.2	19.6-28.6	20.9-27.4	0.10
78 years	6.8-16.0	7.4-16.3	0.10-0.48	0.02-0.35	318.5-390.5	20.0-28.7	20.9-27.2	0.11
79 years	6.9-16.0	7.5-16.3	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
80 years	7.0-16.0	7.5-16.3	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
81 years	7.1-16.0	7.7-16.2	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
82 years	7.2-16.0	7.8-16.2	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
83 years	7.2-16.0	7.9-16.2	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
84 years	7.3-16.0	8.0-16.2	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
85 years	7.3-16.0	8.2-16.2	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11
>85 years	7.4-16.0	8.3-16.2	0.10-0.48	0.02-0.35	317.9-390.6	20.3-28.7	21.0-27.1	0.11

Interpretation

An interpretive report will be provided.

When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (complementation studies, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, complementation studies) or molecular genetic analyses are required.

Cautions

Normal levels may be seen in patients undergoing treatment.

Clinical Reference

1. 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
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. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;40(1):21-48
4. Baric I, Staufner C, Augoustides-Savvopoulou P, Chien YH, Dobbelaere D, Grunert SC. Consensus recommendations for the diagnosis, treatment and follow-up of inherited methylation disorders. J Inherit Metab Dis. 2017;40(1):5-20
5. Morris AA, Kozich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40(1):49-74
6. Sloan JS, Carrillo N, Adams D, Venditti CP. Disorders of intracellular cobalamin metabolism. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated December 16, 2021. Accessed November 29, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1328/
7. Langan RC, Goodbred AJ. Vitamin B12 deficiency: Recognition and management. Am Fam Physician. 2017;96(6):384-389

Performance

Method Description

Total homocysteine, total cysteine, 2-methylcitric acid, methionine, cystathionine and methylmalonic acid are measured by stabile isotope dilution microflow liquid chromatography tandem mass spectrometry.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday, Wednesday, Friday

Report Available

3 to 6 days

Specimen Retention Time

1 week

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.

CPT Code Information

83090
83918
82136
82542 (if appropriate for government payers)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CMMPP	CMMP, P	104535-0

Result ID	Test Result Name	Result LOINC® Value
606110	Interpretation	59462-2
606104	Total Homocysteine	13965-9
606105	Methylmalonic acid	13964-2
606119	2-Methylcitric acid	26904-3
606106	Methionine	20651-6
606107	Total Cysteine	20641-7
606108	Cystathionine	26607-2
606109	Reviewed By	18771-6