

Overview

Useful For

Evaluating children with signs and symptoms of methylmalonic acidemia

Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin deficiency

Method Name

LiquidChromatography-TandemMassSpectrometry(LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Urine

Specimen Required

Patient Preparation: Overnight fast required

Supplies: Urine Tubes, 10 mL (T068)

Container/Tube: Plastic, 10-mL urine tube (T068)

Specimen Volume: 4 mL

Collection Instructions: Collect **second-voided** specimen after an overnight fast.

Forms

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

1.2 mL

Reject Due To

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

Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---------------|--------------------|---------|-------------------|
| Urine | Frozen (preferred) | 28 days | |
| | Refrigerated | 28 days | |

| Specimen Type | Temperature | Time | Special Container |
|---------------|-------------|---------|-------------------|
| | Ambient | 21 days | |

Clinical and Interpretive

Clinical Information

Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria.

MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin.

Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, which includes serum and urine MMA levels.

Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

Reference Values

<3.60 mmol/mol creatinine

Interpretation

In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed.

In adults, moderately elevated values indicate a likely cobalamin deficiency.

Cautions

Diet, nutritional status, and age should be considered in the evaluation of serum or urine methylmalonic acid level.

Clinical Reference

1. Fenton WA, Gravel RA, Rosenblatt DS: Chapter 94. Disorders of propionate and methylmalonate metabolism. In *The Metabolic and Molecular Bases of Inherited Disease*. In Scriver's *The Online Metabolic and Molecular Basis of Inherited Disease (OMBBID)* Edited by D Valle, A Beaudet, B Vogelstein, et al. McGraw-Hill. Accessed 08/17/2017

2. Klee GG: Cobalamin and folate evaluation: Measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. *Clin Chem* 2000;46(B):1277-1283

3. Hussein L, Abdel A, Tapouzada S, Boehles H: Serum vitamin B12 concentrations among mothers and newborns and follow-up study to assess implication on the growth velocity and the urinary methylmalonic acid excretion. Int J Vitam Nutr Res 2009 Sep;79(5-6):297-307

Performance

Method Description

Methylmalonic acid (MMA) is determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) stable isotope dilution analysis. The specimen is mixed with an internal standard (methyl-d3-malonic acid). MMA and d3-MMA are isolated by solid phase extraction. LC-MS/MS is performed using mobile phases and a short C18 column to separate MMA and d3-MMA from the bulk of the specimen matrix. The MS/MS is operated in the multiple reaction monitoring (MRM) negative mode to follow the precursor to product species transitions. Separation of MMA/d3-MMA from the more physiologically abundant succinic acid is accomplished by the careful selection of MRM transitions and optimization of the LC separation. The ratios of the extracted peak areas of MMA to d3-MMA determined by LC-MS/MS are used to calculate the concentration of MMA present in the sample. (Lacey J, Magera MJ, Matern D: Methylmalonic acid quantitation in serum, urine and amniotic fluid: a method modification with benefits. J Am Soc Mass Spectrom 2010:21[5], Supplement 1, S44)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday, Thursday; Continuously until 12 p.m.

Analytic Time

3 days

Maximum Laboratory Time

5 days

Specimen Retention Time

1 week

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

83921

LOINC® Information

| Test ID | Test Order Name | Order LOINC Value |
|---------|---------------------------|-------------------|
| MMAU | Methylmalonic Acid, QN, U | 25116-5 |

| Result ID | Test Result Name | Result LOINC Value |
|-----------|---------------------------|--------------------|
| 80290 | Methylmalonic Acid, QN, U | 25116-5 |