Methylmalonic Acid and Methylcitric Acid, Quantitative, Dried Blood Spot

**Condition Description**

Methylmalonic aciduria (MMA) is an autosomal recessive inborn error of organic acid metabolism due to several etiologies. Partial or complete deficiency of the enzyme L-methylmalonyl-CoA mutase leads to isolated methylmalonic aciduria. Methylmalonyl-CoA mutase deficiency may present with lethargy, recurrent vomiting, hepatomegaly, metabolic acidosis, encephalopathy, and may lead to multiorgan failure. Methylmalonyl-CoA mutase requires adenosylcobalamin, a vitamin B12 derived prosthetic group, to function. Therefore MMA is also seen in patients with vitamin B12 deficiency. Causes of B12 deficiency include: genetic defects of Cbl A, B, C, D or F; vitamin B12 absorption and transport deficiencies; or dietary restriction of meat.

Most forms of MMA related to deficiencies of vitamin B12 or derived compounds are responsive to vitamin B12 supplementation. Affected infants may show failure to thrive, chronic or episodic acidemia, benign persistent methylmalonic aciduria, or developmental delay. These symptoms may be associated with episodes of infection or stress. The major biochemical feature of MMA is elevation of propionyl carnitine, methylmalonic acid and methylcitric acid. Patients with Cbl C, D, or F may have combined methylmalonic aciduria and homocystinuria. The prevalence of MMA is approximately 1 in 30,000 newborns.

Propionic acidemia (PA) is an autosomal recessive disorder of organic acid metabolism caused by a defect of propionyl-CoA carboxylase (PCC). PCC catalyzes the carboxylation of propionyl-CoA to D-methylmalonyl-CoA in the catabolic pathway of odd-numbered carbon fatty acids and amino acids, i.e. isoleucine, valine, threonine, and methionine. The major biochemical features of PA include mild to severe ketoadidosis, hyperammonemia, hyperglycinemia, and a diagnostic urine organic acid profile (3-hydroxypropionate, methylcitrate, propionylglycine, and tiglylglycine). The common clinical presentation includes frequent vomiting, lethargy, refusal to feed, and hypotonia. In most of the patients there is a neonatal clinical onset associated with development delay and neurological impairment, but late-onset patients are also described with a milder course.

Conventional treatment of PA consists of dietary restriction of protein, increase of caloric intake, avoidance of long-fasting periods and carnitine supplementation and may include oral antibiotic therapy.

**GeneReviews Summaries:**

- **Methylmalonic aciduria (MMA)**
- **Propionic acidemia (PA)**

**Indications**

Second-tier assay for newborn screening when abnormal propionyl carnitine or methionine concentrations are detected in an initial newborn screen.

This test is indicated for:

- Individuals with low methionine level by routine NBS
- Individuals with C3 elevation by routine NBS
- Individuals suspected to have methylmalonic acidemia (MMA), propionic acidemia (PA), or holocarboxylase deficiency

**Methodology**

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

**Detection**

Comprehensive interpretation takes into consideration any available clinical and dietary information and other lab results, provides possible differential diagnoses, recommendations for additional biochemical testing, and confirmatory studies if indicated.

**Reference Range**

- MMA reference range: 0 - 0.84 µM
- MCA reference range: 0 - 0.38 µM

A metabolic disorder is suspected when MMA >5 µM or MCA >1 µM.

**Specimen Requirements**
Submit only 1 of the following specimen types

**Type: Dried Blood Spot**

**Specimen Requirements:**

Peripheral blood from finger prick or heel stick spotted on filter paper, completely saturating the circle. Air dry sample.

**Specimen Collection and Shipping:** Do not expose specimen to heat or direct sunlight. Keep the specimen dry. Ship sample at room temperature with overnight delivery.

**Special Instructions**

Please include a list of current medications.

**Related Tests**

**Biochemical**

- Organic Acids Quantitative Analysis (OA)
- Acylcarnitine Profile (AR)
- Homocysteine, Total (HO)
- Homocysteine, Total, Dried Blood Spot (BHOBS)
- Methylmalonic Acid Quantitation (MQ)
- NBS Follow-up: Elevated C3 (BNBSF)

**Molecular**

- Methylmalonic Aciduria (MMA): Methylmalonyl CoA Mutase (MUT) Full Gene Sequencing (DH)
- Methylmalonic Aciduria (MMA): Methylmalonyl CoA Mutase (MUT) Gene Deletion/Duplication (NK)
- Methylmalonic Aciduria (Cbl A/Cbl B): MMAA and MMAB Full Genes Sequencing (MU)
- Methylmalonic Aciduria (Cbl A/Cbl B): MMAA and MMAB Genes Deletion/Duplication (NJ)
- Methylmalonic Aciduria and Homocystinuria, Cbl Type: MMACHC Full Gene Sequencing (XU)
- Methylmalonic Aciduria and Homocystinuria, CblC Type: MMACHC Gene Deletion/Duplication (XW)
- Propionic Acidemia (PA): PCCA and PCCB Full Gene Sequencing (KK)
- Propionic Acidemia (PA): PCCA and PCCB Gene Deletion/Duplication (KI)