Methylmalonic Aciduria:  *MUT* Gene Deletion/Duplication

**Test Code:** NK  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

### Condition Description

Methylmalonic aciduria (MMA) is an autosomal recessive inborn error of organic acid metabolism resulting from partial or complete deficiency of the enzyme L-methylmalonyl CoA mutase. The most common form of MMA is mutase deficient MMA, which may present lethargy, recurrent vomiting, hepatomegaly, metabolic acidosis, encephalopathy, and may lead to multiorgan failure. Other forms of MMA may be B12 responsive, and affected infants may show failure to thrive, chronic or episodic acidemia, benign persistent methylmalonic aciduria, or developmental delay. These symptoms may be associated with times of infection or stress. Patients with defects in the synthesis of adenosyl cobalamin (CbiA and CbiB) generally show a decrease in urine and blood concentration of methylmalonic acid in response to B12 supplementation. The prevalence of MMA is approximately 1 in 30,000 newborns.

Methylmalonyl CoA mutase catalyzes the isomerization of methylmalonyl CoA into succinyl-CoA. The coenzyme adenosylcobalamin (AdoCbl) is also required for this reaction. Mutations in the *MUT* gene cause mutase-deficient MMA. *MUT* is a nuclear gene (6q21) that codes for the mitochondrial enzyme, methylmalonyl CoA mutase. Based on enzymatic activity in cultured fibroblasts, two phenotypic variants of mutase deficient MMA have been defined. The mut0 phenotype has no detectable enzymatic activity and is associated with severe symptoms in patients. The mut- phenotype has residual activity that is increased by supplementation of hydroxycobalamin and is associated with variable severity.

Apart from primary deficiency of mutase activity, insufficient metabolism of cobalamin can also result in deficient mutase activity. *MMAA* and *MMAB* genes are involved in the adenosylcobalamin metabolism (associated with the cblA and cblB complementation groups of MMA, respectively). (Refer to *MMAA* and *MMAB* gene sequencing for more information.)

### Genes

**MMUT**

### Indications

This test is indicated for:

- Clinical symptoms of possible non-B12 responsive MMA
- Follow up to abnormal newborn screening results suggestive of MMA
- Clinical symptoms of MMA, with negative *MMAA/MMAB* gene sequencing
- Family members who are at risk to be carriers of MMA, when the proband is unavailable for testing.

Sequencing is not appropriate for prenatal samples in which familial mutations have not been identified.

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

### Detection

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Specimen Requirements

*Submit only 1 of the following specimen types*

#### Type: DNA, Isolated

**Specimen Requirements:**

- Microtainer
- 3µg Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

#### Type: Whole Blood (EDTA)

**Specimen Requirements:**

- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood
Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions
Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

Related Tests
- Organic Acid Analysis (OA) is used in the diagnosis of patients with MMA
- Methylmalonic Acid Quantitation (MQ) is used in diagnosis and follow up of propionate and methylmalonic disorders, as well as defects of cobalamin synthesis; it can also detect acquired cobalamin, and/or folate deficiency
- MMAA/MMAB (MU) Gene Sequencing may be considered in patients with a biochemical diagnosis of MMA but with normal MUT gene sequencing
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Prenatal testing is available to couples who are confirmed carriers of gene mutations. Please contact the laboratory genetic counselor prior to sending a specimen.