

Methylmalonic Acidemia Sequential Testing via *MUT*, *MMAA*, *MMAB* Gene Sequencing (Test #310)

Brief Description of Clinical Features: Methylmalonic acidemia (MMA) is typically a severe disease with onset in infancy. Patients may present with lethargy, vomiting, hepatomegaly, acidosis, hypoglycemia and neutropenia. Many patients die in childhood; those that survive often experience neurological and renal complications. Milder forms of the disease are also known. Today, many cases are detected through routine neonatal screening with tandem mass spectrometry. For more information, see Venditti GeneReviews 2007 (www.genetests.org), and the Organic Acidemia Association (www.oaanswers.org). Methylmalonyl-CoA mutase, encoded by *MUT*, catalyzes the last step the breakdown of certain amino acids (met, ile, thr, val), odd-numbered chain length fatty acids, and propionic acid from gut flora. *MUT* mutations are the most common cause of MMA. Vitamin B₁₂ responsive (or cbl type) MMA is caused by defective metabolism of adenosylcobalamin (AdoCbl; vitamin B₁₂), the cofactor for methylmalonyl-CoA mutase. Three distinct genetic causes of cbl type MMA have been identified; cblA, cblB and cblH. CblA type MMA (OMIM 251100) has the most favorable clinical outcome (Fenton et al., in: Scriver, *Metabolic Basis of Inherited Disease*, 2165-2190, 2001), and is thought to be caused by defective mitochondrial transport of cbl (Yang et al., *Mol Gen and Metab* 82:329-333, 2004). CblB type MMA (OMIM 251110) results from deficiency of cob(I)alamin adenosyltransferase, the enzyme that catalyzes the final step in synthesis of adenosylcobalamin.

Genetics: Methylmalonic acidemia is an autosomal recessive disease. The *MUT* gene encodes the methylmalonyl-CoA mutase enzyme. About 200 causative *MUT* mutations have been reported to date and over half are missense. The *MMAA* gene product is required for transport of cbl into mitochondria where adenosylcobalamin synthesis occurs. *MMAB* encodes cob(I)alamin adenosyltransferase. Most reported *MMAA* and *MMAB* mutations are missense, but small deletions, small insertions and splice site mutations have been described.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *MUT*, *MMAA* and *MMAB* genes. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. The test is performed sequentially with *MUT* sequenced first. If likely causative mutations are found in *MUT*, we stop there; otherwise we go on to sequence both *MMAA* and *MMAB*. We will sequence any single or pair of exons for family members of patients or to confirm research results (\$190-340).

Reference Sequences:

Gene:	Genomic: NC_	mRNA: NM_	Protein: NP_
<i>MUT</i>	000006.10	000255.1	000246.1
<i>MMAA</i>	000004.10	172250.1	758454.1
<i>MMAB</i>	000012.10	052845.4	443077.1

Indications for Test: All methylmalonic acidemia patients and their family members are candidates for this test. If the patient's cells lack mutase activity and there is no response to cobalamin in culture or to therapeutic vitamin B₁₂, then testing should focus on *MUT*. *MMAA* and *MMAB* should be considered in patients with cobalamin-responsive mutase activity *in vitro* and/or successful vitamin B₁₂ treatment.

Sensitivity of Test: Martinez et al. (*Mol Gen and Metab* 84:317-325, 2005) evaluated 25 MMA patients and found *MUT* mutations in 13 patients, *MMAA* mutations in 7, and *MMAB* mutations in 2.

Turn Around Time: Maximum of 40 days for each gene, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequential Sequencing of: *MUT*, *MMAA*, *MMAB*

CPT Codes	<i>MUT</i>	<i>MMAA</i>	<i>MMAB</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 240 (x12)	\$ 160 (x6)	\$ 120 (x8)	\$ 490 (x26)
83904	\$ 350 (x12)	\$ 180 (x6)	\$ 220 (x8)	\$ 740 (x26)
83894	\$ 50 (x1)	\$ 50 (x1)	\$ 50 (x1)	\$ 110 (x1)
83912	\$ 80 (x1)	\$ 80 (x1)	\$ 80 (x1)	\$ 140 (x1)
Totals:	\$ 790	\$ 490	\$ 540	\$ 1,550*

*When two or more of the genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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