

3-Methylcrotonyl-CoA Carboxylase Deficiency via *MCCC1* and *MCCC2* Gene Sequencing Sequential (Standard) Test – Test #320; Tier 1 (*MCCC2*) – Test #321; Tier 2 (*MCCC1*) – Test #322

Brief Description of Clinical Features: 3-Methylcrotonyl-CoA Carboxylase (MCC) Deficiency (OMIM 210200 and 210210) is a defect in the catabolism of the amino acid leucine. MCC is the next enzyme after isovaleryl-CoA dehydrogenase in the degradation pathway. MCC deficiency leads to abnormally high levels of 3-methylcrotonylglycine in the urine and 3-hydroxyisovalerylcarnitine in the blood. MCC Deficiency is one of the most frequent disorders detected through neonatal screening with tandem mass spectrometry. The most severe forms of MCC Deficiency have onset in infancy and are characterized by episodes of vomiting, lethargy and muscle weakness. These episodes can lead to seizures, coma and death. A variety of other, mostly neurological, symptoms have been reported. For more information, see Seashore GeneReviews 2006 (www.genetests.org); Stadler et al. Hum Mut 27:748-759, 2006; and the Organic Acidemia Association (www.oaanews.org).

Genetics: MCC Deficiency is an autosomal recessive disorder. The MCC enzyme has two subunits, α and β , encoded by the *MCCC1* (also called *MCCA*) and *MCCC2* (*MCCB*) genes, respectively. Mutations in either gene can lead to MCC Deficiency. No differences in clinical features have been reported for mutations in *MCCC1* versus *MCCC2*. About 30 different causative mutations have been reported in *MCCC1* and 45 in *MCCC2* (Gallardo et al. Am J Hum Genet 68:334-346, 2001; Baumgartner et al. J Clin Invest 107:495-504, 2001; Dantas et al. Hum Mut 26:164, 2005; Stadler et al. 2006). In both genes, the causative mutations are about equally split between missense and nonsense/frameshift/splicing. No common mutations have been reported. Mutations are distributed throughout the lengths of the genes. Although nearly all MCC Deficiency patients detected by neonatal screening carry likely causative mutations, it appears that many such patients, perhaps even the great majority, will not experience significant health problems (Dantas et al. 2005; Stadler et al. 2006). The genetic or non-genetic factors which exert such strong control over the expressivity of the mutations are currently unknown.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 19 exons of the *MCCC1* gene and all 17 exons of the *MCCC2* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. Either gene test may be ordered separately.

Reference Sequences:

Gene:	Genomic: NC_	mRNA: NM_	Protein: NP_	mRNA and Protein: CCDS
<i>MCCC1</i>	000003.10	020166.2	064551.2	3241.1
<i>MCCC2</i>	000005.8	022132.3	071415.1	34184.1

Indications for Test: All MCC Deficiency patients are candidates for this test. In cases where DNA from an affected child is unavailable, we will sequence the genes in parents or other family members. We will also sequence any single exon or pair of exons in family members of patients with known mutations, and to confirm research results (\$190-340 charge).

Sensitivity of Test: Stadler et al. 2006 reported detecting two causative mutations by sequencing the *MCCC1* and *MCCC2* genes in 28 out of 28 patients.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequential Sequencing of: *MCCC2* and *MCCC1*:

Gene	CPT Codes						Totals
	83890	83891	83898	83904	83894	83912	
<i>MCCC2</i>	\$ 30 x1	\$ 40 x1	\$ 220 x17	\$ 330 x17	\$ 80 x1	\$ 140 x1	\$ 840
<i>MCCC1</i>	\$ 30 x1	\$ 40 x1	\$ 280 x19	\$ 420 x19	\$ 80 x1	\$ 140 x1	\$ 990
Both Genes	\$ 30 x1	\$ 40 x1	\$ 500 x36	\$ 750 x36	\$ 160 x1	\$ 280 x1	\$ 1,690

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

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