

**Comprehensive
Molecular Testing
for Fatty Acid
Oxidation Disorders**

A Guide for Clinicians

 **METABOSEQ**

 **Cincinnati
Children's**

Cincinnati Children's Hospital Molecular Genetics Laboratory introduces

MetaboSeq, our next-generation sequencing panel of 19 genes (see Table 1) associated with fatty acid oxidation disorders (FAOD). MetaboSeq is the first test of its kind for diagnosing any of a large number of FAOD which often have overlapping clinical presentations. Fatty acid oxidation disorders are a group of inherited metabolic conditions. Mutation(s) in any one of a number of specific genes cause defective enzyme production in this key metabolic pathway. During times of fasting, illness, or exertion, fatty acids are normally mobilized in the body, but, in patients with FAOD, an enzyme defect results in the diminished ability to break down fatty acids into the energy necessary to overcome these stressors. Affected patients may show FAOD symptoms (liver failure, rhabdomyolysis, muscular hypotonia, cardiomyopathy with or without arrhythmias and/or renal tubular acidosis) within the first days to weeks of life; these disorders are often fatal if not detected early [Strauss et al. 2009]. Early initiation of treatment leads to good outcomes in most instances.

GENETICS of FAOD: Newborn screening has tremendously aided the early diagnosis of FAOD. When an abnormal newborn screening result indicates a specific disorder, Sanger sequencing of the specific gene of interest can identify the underlying genetic cause of the disorder in many patients. However, biochemical screening results may show measurements that overlap with several conditions (e.g. acylcarnitine screening

uncovers cases of MCADD, M/SCHADD, MCKATD and glutaric acidemia type 2 alike) [Lindner et al. 2010]. Additionally, significant genetic heterogeneity has been reported for long-chain fatty acid oxidation disorders [Spiekerkoetter et al. 2010]. These factors highlight the utility, in some cases, of a comprehensive analysis of multiple genes involved in fatty acid oxidation. The MetaboSeq panel includes FAOD genes in the carnitine cycle and beta-oxidation pathway; as well as other integral pathway genes, including electron transporters (*ETFA*, *ETFB*, *ETFDH*), one gene involved in ketone synthesis (*HMGCL*), and two genes with phenotypic overlap with traditional FAODs (*GLUD1* and *TAZ*) (see Figure 2).

INDICATIONS for MetaboSeq:

- Abnormal newborn screen
- Unexplained neonatal hypoglycemia
- Recurrent maternal fatty liver of pregnancy
- Reye syndrome
- Rhabdomyolysis/skeletal myopathy
- Cardiomyopathy and/or arrhythmias
- Other nonspecific symptoms of FAOD including:
 - liver failure
 - vomiting
 - lethargy
 - seizures
 - coma

Note: Patients with acylcarnitine results or other clinical findings indicating a specific metabolic syndrome may benefit from molecular testing for mutations in that particular gene prior to MetaboSeq testing.

Table 1. The MetaboSeq panel for fatty acid oxidation disorders includes tests for all of the genes included here.

Gene	Disorder	Gene	Disorder
<i>ACAD9</i>	acyl-CoA dehydrogenase-9 (ACAD9) deficiency	<i>HADH</i>	short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency
<i>ACADM</i>	medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	<i>HADHA</i>	long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency or general trifunctional protein (TFP) deficiency
<i>ACADS</i>	short-chain acyl-CoA dehydrogenase (SCAD) deficiency	<i>HADHB</i>	general trifunctional protein (TFP) deficiency or isolated mitochondrial long-chain ketoacyl-CoA thiolase (LKAT) deficiency
<i>ACADVL</i>	very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	<i>HMGCL</i>	3-hydroxymethyl-3-methylglutaryl-CoA lyase (HMG-CoA lyase deficiency)
<i>CPT1A</i>	carnitine palmitoyltransferase 1 (CPT1) deficiency	<i>HSD17B10</i>	17-beta-hydroxysteroid dehydrogenase X (HSD10) deficiency
<i>CPT2</i>	carnitine palmitoyltransferase 2 (CPT2) deficiency	<i>PPARG</i>	peroxisome proliferator-activated receptor-gamma (PPAR-g) ligand resistance syndrome (PLRS) or familial partial lipodystrophy type 3
<i>ETFA</i>	multiple acyl-CoA dehydrogenation (MAD) deficiency	<i>SLC22A5</i>	primary carnitine deficiency
<i>ETFB</i>	multiple acyl-CoA dehydrogenation (MAD) deficiency	<i>SLC25A20</i>	carnitine-acylcarnitine translocase (CACT) deficiency
<i>ETFDH</i>	multiple acyl-CoA dehydrogenation (MAD) deficiency	<i>TAZ</i>	Barth syndrome or familial isolated non-compaction of the left ventricular myocardium
<i>GLUD1</i>	congenital hyperinsulinic hyperammonemia (HI/HA) syndrome		

Clinical utility of testing: A genetic diagnosis of an FAOD using MetaboSeq can assist in the treatment and management of a patient, provide prognostic information about the patient's condition, as well as supply information on which to base accurate genetic counseling and further testing recommendations for at-risk family members, perhaps before symptoms appear.

Figure 1. Diagnostic algorithm for fatty acid oxidation disorders.

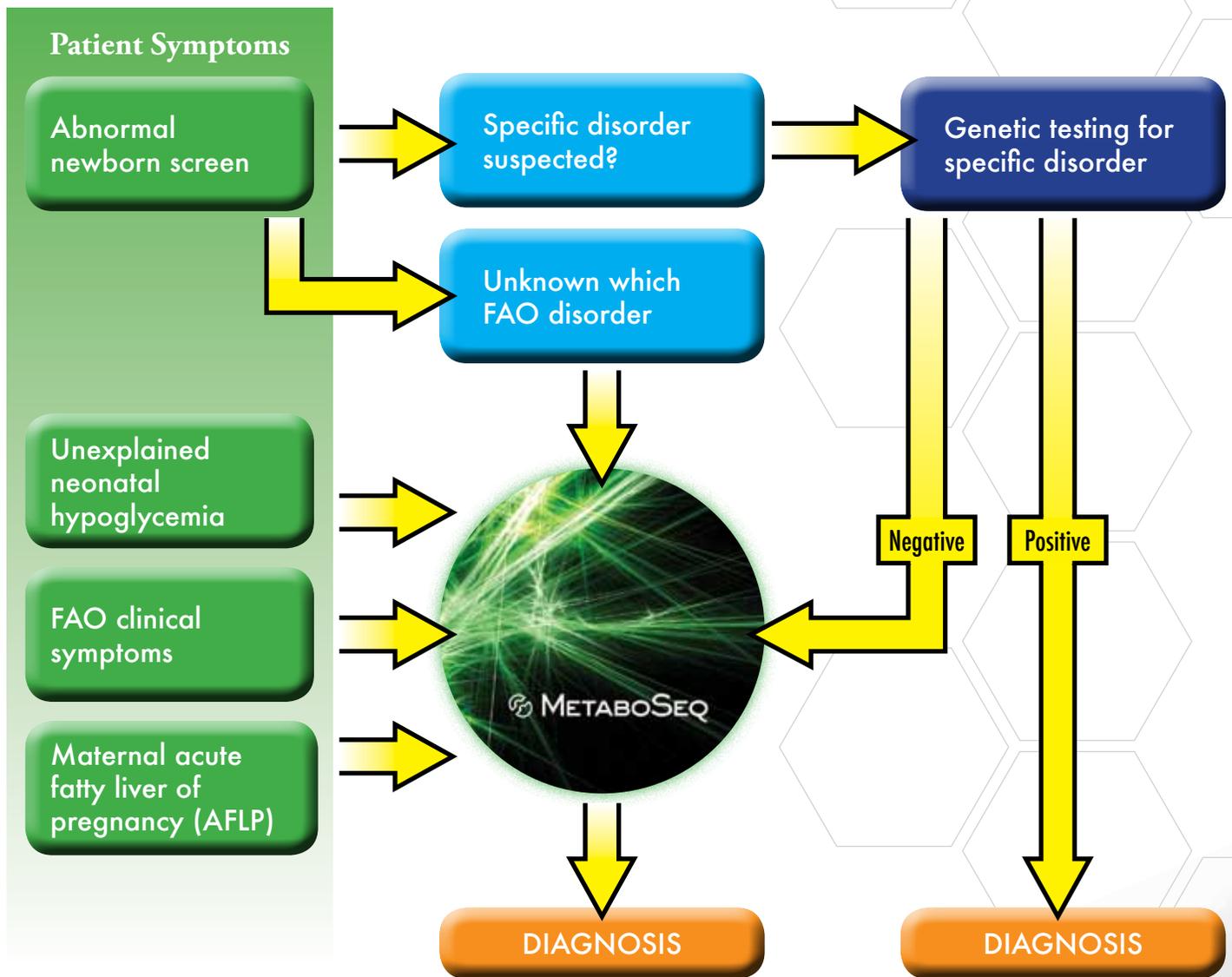
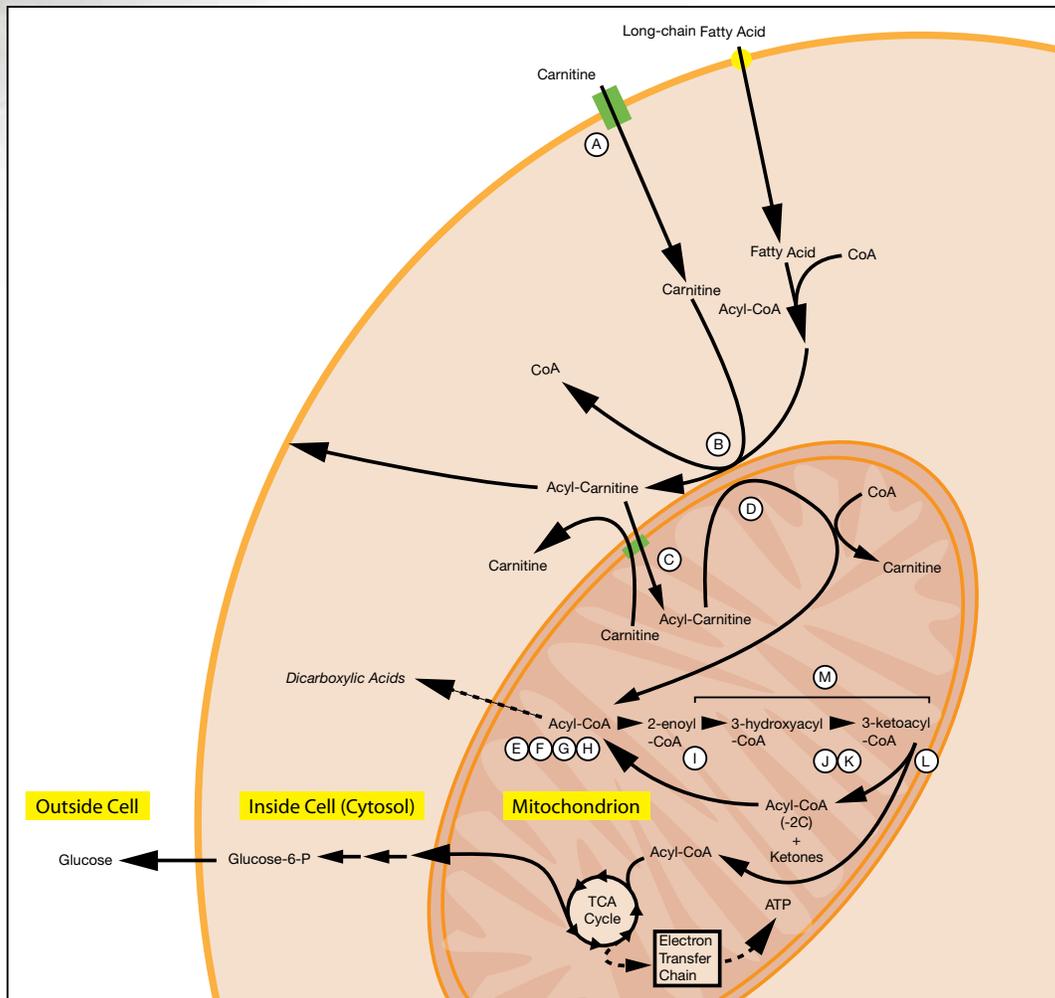


Figure 2. Pathway for mitochondrial fatty acid beta-oxidation. The letters represent key enzymatic steps and specific enzyme and corresponding gene names are in the key below the diagram.



KEY

- | | | |
|---------------------|-----------------------------------|------------------------|
| (A) SLC22A5 (OCTN2) | (F) ACADM (MCAD) | (K) HADH (SCHAD) |
| (B) CPT1A (CPT1) | (G) ACADS (SCAD) | (L) HADHB (LCKAT, TFP) |
| (C) SLC25A20 (CACT) | (H) ACAD9 (ACAD9) | (M) (TFP) |
| (D) CPT2 (CPT2) | (I) ECHS1 (2-enoyl-CoA hydratase) | |
| (E) ACADVL (VLCAD) | (J) HADHA (LCHAD, TFP) | |

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