Fatty Acid Oxidation Disorders Panel

Panel Gene List: *ACADM, ACADS, ACADVL, CPT1A, CPT2, ETFA, ETFB, ETFDH, GLUD1, HADHA, HADHB, HMGCL, HMGCS2, SLC22A5 and SLC25A20*

Clinical Features:
Mitochondrial fatty acid oxidation is the principle pathway for energy production during times of increased energy demand such as fasting, illness and exercise. During fasting when glucose supplies are lowered, long-chain fatty acids stored as triglycerides in fat tissue are released by lipases and activated to acyl-CoA esters that are transported into the mitochondria via the carnitine shuttle. Once inside the mitochondria, several chain-length specific enzymes shorten acyl-CoAs, two carbon atoms at a time, via β-oxidation cycles. Long-chain compounds are metabolized at the inner mitochondrial membrane, while medium and short-chain compounds are metabolized in the mitochondrial matrix. Defects in this process result in disorders of fatty acid oxidation.

The clinical spectrum of fatty acid oxidation disorders ranges from asymptomatic individuals to severely affected patients with complications including hepatic encephalopathy, myopathy, cardiomyopathy, neuropathy and sudden death. In general, fatty acid oxidation disorders present in the following ways. The hepatic presentation is severe with onset in infancy or the neonatal period with hypoketotic hypoglycemia and a Reye-like syndrome. Also during infancy, patients may present with cardiac symptoms including dilated or hypertrophic cardiomyopathy and arrhythmias. Alternatively, patients can present with a milder, later onset disease characterized by exercise-induced myopathy and rhabdomyolysis. Some patients display combinations of these presentations. Additionally, fatty acid oxidation defects have been associated with sudden infant death.[1] Based on newborn screening programs in Australia, Germany and the United States the combined incidence of all fatty acid oxidation disorders is approximately 1 in 9,300.[2]

Most fatty acid oxidation disorders are associated with distinct plasma acylcarnitine profiles and enzymatic analysis is also available for many to determine the specific defect.[3] However, patients with mild or atypical disease presentations may show no abnormalities by acylcarnitine profile or enzymatic analysis.[3] Variant analysis may help to confirm the diagnosis and in some cases genotype/phenotype correlations are possible.[4]

Inheritance Pattern/Genetics:
Autosomal recessive, except *GLUD1* which is autosomal dominant

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Clinical Sensitivity:
Based on the sensitivity of variant analysis for the individual genes, it is estimated that this panel would detect a pathogenic variant in 75% to greater than 95% of patients with a fatty acid oxidation disorder due to pathogenic variants in one of the 15 genes.

Gene	Protein	Inheritance	Disease Associations
ACADM	Acyl-CoA dehydrogenase, medium-chain	Autosomal Recessive	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
ACADS	Acyl-CoA dehydrogenase, short-chain	Autosomal Recessive	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency
ACADVL	Acyl-CoA dehydrogenase, very long-chain	Autosomal Recessive	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
CPT1A	Carnitine palmitoyltransferase I, liver	Autosomal Recessive	Carnitine palmitoyltransferase IA deficiency
CPT2	Carnitine palmitoyltransferase II	Autosomal Recessive	Carnitine palmitoyltransferase II (CPT2) deficiency

Gene	Protein	Inheritance	Disease Associations
ETFA	Electron transfer flavoprotein, alpha peptide	Autosomal Recessive	Glutaric aciduria II (GAII)
ETFB	Electron transfer flavoprotein, beta peptide	Autosomal Recessive	Glutaric aciduria II (GAII)
ETFDH	Electron transfer flavoprotein dehydrogenase	Autosomal Recessive	Glutaric aciduria II (GAII)
GLUD1	Glutamate dehydrogenase 1	Autosomal Dominant	Glutamate dehydrogenase I deficiency
HADHA	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit	Autosomal Recessive	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)/ Mitochondrial trifunctional protein (MTP) deficiency
HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, beta subunit	Autosomal Recessive	Mitochondrial trifunctional protein (MTP) deficiency
HMGCL	3-hydroxy-3-methylglutaryl-CoA lyase	Autosomal Recessive	HMG CoA lyase deficiency (3-Hydroxy-3-methylglutaryl CoA lyase deficiency
HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2	Autosomal Recessive	HMG-CoA synthase-2 deficiency (3-Hydroxy-3-methylglutaryl-CoA synthase 2 deficiency
SLC22A5	Solute carrier family 22 (organic cation transporter), member 5	Autosomal Recessive	Primary/systemic carnitine deficiency
SLC25A20	Solute carrier family 25 (carnitine/acylcarnitine translocase), member 20	Autosomal Recessive	Carnitine-acylcarnitine translocase deficiency

References:

1. Houten, S. and Wanders, R. (2010) J Inherit Metab Dis 33:469-477
2. Lindner, M., et al., (2010) J Inherit Metab Dis 33:521-526
3. Wanders et al., (2010) J Inherit Metab Dis 33:479-494
4. Spiekerkoetter, U. and Mayatepek, E., (2010) J Inherit Metab Dis 33:467-468
5. Bennett S.(2004) Pharmacogenomics 5:433-8