Riboflavin Transporter Deficiency and Related Disorders Panel

PANEL GENE LIST
SLC52A1, SLC52A2, SLC52A3, SLC25A32, FLAD1, ETFDH, ETFA, ETFB, ACAD9

CLINICAL FEATURES
Individuals with riboflavin transporter deficiency (also known as Brown-Vialetto-Van Laere syndrome) due to variants in the SLC52A2 and SLC52A3 genes typically present in infancy or childhood before age 8 years, but can also present as late as the third decade. Symptoms may include motor neuronopathy (with muscle weakness and wasting and diaphragm paralysis causing respiratory insufficiency) cranial nerve deficits (sensorineural hearing loss, bulbar palsy, reduced vision and/or optic atrophy), gait ataxia, and feeding difficulties. Infants left untreated typically become ventilator dependent and expire with the first few years of life. Some differences have been reported in the neurologic phenotype in individuals with riboflavin transporter deficiency due to variants in SLC52A2 versus SLC52A3, in particular early onset weakness in the upper limbs and an ataxic gait in patients with SLC52A2 variants. An improvement in clinical symptoms has been shown with high dose riboflavin supplementation. Acylcarnitine profiles with the accumulation of short and medium chains are abnormal in 50-60% of individuals with riboflavin transporter deficiency and quickly normalize with riboflavin supplementation.

The features of riboflavin transporter deficiency can overlap with those of other metabolic disorders, some of which may also respond to riboflavin supplementation. Many individuals with multiple acyl-CoA dehydrogenase deficiency due to pathogenic variants in ETFDH and some individuals with pathogenic variants in FLAD1 and ACAD9 genes have been reported to respond to riboflavin. The SLC25A32 gene has been described in association with riboflavin-responsive exercise intolerance and in an individual with a muscular phenotype and exercise intolerance that later progressed to a severe neuromuscular disorder. Both individuals also had biochemical features of multiple acyl-CoA dehydrogenase deficiency.

GENETICS
All of the disorders tested for in this panel are inherited in an autosomal recessive manner with the exception of riboflavin deficiency due to variants in SLC52A1 for which only a single case has been reported.

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-CNVo). 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. For the SLC52A1 gene, sequencing but not deletion/duplication analysis, is performed. 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.

REFERENCES: