**Test Information Sheet**

**MMACHC Gene Analysis in Methylmalonic Aciduria and Homocystinuria, cobalamin C (cblC) Type**

**Clinical Features:**
Methylmalonic aciduria and homocystinuria, cblC type, is a defect in B12 metabolism. Affected individuals may present with severe early-onset disease that includes developmental delay, megaloblastic and macrocytic anemia, feeding difficulties, failure to thrive, microcephaly, lethargy, and additional neurologic symptoms such as seizures, hypotonia, intellectual disability, developmental delay, ataxia, optic atrophy, retinal degeneration, and pigmentary retinopathy.\(^1\) Clinical features in late-onset cases may include hemolytic uremic syndrome, pulmonary hypertension, megaloblastic anemia, psychiatric disturbance, cognitive impairment, dementia, white matter lesions and cerebral atrophy, spinal cord degeneration, anorexia, irritability, fatigue, myelopathy, thromboembolic events, and nephropathy (including renal thrombotic microangiopathy).\(^1\)\(^-\)\(^4\)

**Genetics:**
Methylmalonic aciduria and homocystinuria, cblC type, is due to pathogenic variants in the **MMACHC** gene, which cause decreases in adenosylcobalamin and methylcobalamin and deficient activity of both methylmalonyl-CoA mutase and methionine synthase/methyltetrahydrofolate: homocysteine methyltransferase. **MMACHC** pathogenic variants cause increases in homocystine and methylmalonate; the methylmalonate concentration is usually less than that in methylmalonyl-CoA mutase deficiency. Other more rare forms of methylmalonic aciduria and homocystinuria have been identified by complementation studies, including cblD (**MMADHC**), cblF (**LMBRD1**), and cblJ (**ABCD4**) deficiency.\(^5\)\(^-\)\(^8\) **MMACHC** is located on chromosome 1p34.1.

**Inheritance Pattern:**
Autosomal Recessive

**Test Methods:**
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the **MMACHC** gene 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 the reference sequence 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.

**Variant Spectrum:**
Missense, nonsense, and splice-site variants, small deletions/duplications, gross deletions, and variants affecting the start codon have been reported. One variant, c.271dupA, was observed in 40% of alleles of patients with methylmalonic acidemia and homocystinuria, cblC and found in the homozygous state in approximately 22% of patients. This variant was found in several different ethnic groups.

**References:**