Name of Test/Panel

PANEL GENE LIST
FAH, HPD and *TAT*

CLINICAL AND FEATURES
Tyrosinemia types I, II and III are all inborn errors of tyrosine metabolism. Tyrosinemia type I, II and III are caused by pathogenic variants in the *FAH, TAT* and *HPD* genes respectively. The *FAH* gene encodes fumarylacetoacetase that catalyzes the hydrolysis of fumarylacetoacetate into fumarate and acetoacetate, the final step in the tyrosine degradation pathway. The *TAT* gene encodes tyrosine aminotransferase that catalyzes the conversion of tyrosine to p-hydroxyphenylpyruvate, and the *HPD* gene encodes 4-hydroxyphenylpyruvic acid dioxygenase that catalyzes the second step of the tyrosine degradation pathway: the conversion of 4-hydroxyphenylpyruvic acid to homogentisate. All three disorders can present with elevated blood tyrosine levels which may be detected on newborn screening and elevated tyrosine derivatives in urine. Elevated succinylacetone in urine or blood is a pathognomonic marker for tyrosinemia type I.

Tyrosinemia type I (*FAH* gene) is the most well described of the three disorders with untreated patients presenting in infancy with severe liver involvement or presenting in the first year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets. Neurological crisis that can include change in mental status, abdominal pain, peripheral neuropathy and/or respiratory failure may also occur. Patients have a high risk of developing hepatocarcinoma, even at a very young age.[1] Tyrosinemia type II (*TAT* gene) is characterized by keratitis, palmoplantarkeratosis, ophthalmologic involvement and intellectual disability. The skin is affected in approximately 80% of reported cases, the eye in approximately 75% and mental retardation is present in over 60% of reported cases.[2] Eye manifestations usually occurbefore the skin lesions develop and include photophobia, redness and pain.2Neurodevelopmental disability is variable, ranging from severe retardation to a mild decrease in intelligence.[2] Tyrosinemia type III (*HPD* gene) is the rarest of the three disorders with few individuals described. Like type II, there is no liver involvement but skin and ocular changes have been described. Affected patients also have neurologic findings including neurodevelopmental delay and/or intermittent ataxia.[3,4] Another rare disorder of tyrosine metabolism has also been attributed to pathogenic variants in the *HPD* gene, hawkinsinuria. Individuals with hawkinsinuria may be asymptomatic or exhibit failure to thrive, episodes of tyrosinemia and metabolic acidosis that respond to protein restriction. Symptoms improve within the first year of life.[4,5] Patients with hawkinsinuria may also be detected by newborn screening.

INHERITANCE PATTERN/GENETICS
Autosomal recessive

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.

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