Skeletal Dysplasia: Osteogenesis Imperfecta Panel
Sequence Analysis and Deletion/Duplication Testing of 15 Genes

Panel Gene List:
BMP1, COL1A1, COL1A2, CRTAP, FKBP10, IFITM5, P3H1(LEPRE1), PLOD2, PLS3, PP1B, SERPINF1, SERPINH1, SP7, TMEM38B, and WNT1.

Clinical Features:
Osteogenesis Imperfecta (OI) is characterized by bone fragility and consequent susceptibility to bone fractures. The severity of OI can range from severe perinatal lethal to asymptomatic with mild predisposition to fractures and a normal lifespan. Other common characteristics include dentinogenesis imperfecta, blue sclerae, short stature and hearing loss in adulthood. The most lethal form of OI is type II, which is characterized by compressible thin calvaria, severe micromelia and bowing of long bones with multiple fractures and a narrow thorax. Together, all types of OI have a combined prevalence of between 1 in 15,000 and 1 in 30,000 births with about 90% of cases caused by variants in either COL1A1 or COL1A2.

About 90% of all pathogenic variants causing Osteogenesis Imperfecta are within COL1A1 or COL1A2. At least 1832 different OI-causing pathogenic variants have been identified, of which 682 are glycine substitution pathogenic variants in the triple helix domain of the proteins and 150 are splice site pathogenic variants. Pathogenic variants in these two genes can lead to variable phenotypes ranging in severity from mild to lethal. Other genes which can contain pathogenic variants causing OI, may also cause a variable phenotype, while certain genes are known to correlate with certain levels of severity. For example, pathogenic variants in SERPINH1 and BMP1 are associated with a severe phenotype, while pathogenic variants in IFITM5 and SP7 lead to a moderate phenotype, and pathogenic variants in PLS3 produce a mild phenotype. Additionally, FKBP10 pathogenic variants are specifically associated with progressive deformity and contractures.

Inheritance Pattern/Genetics:
Osteogenesis Imperfecta due to pathogenic variants in COL1A1, COL1A2, and IFITM5 is an autosomal dominant condition. Autosomal recessive osteogenesis imperfecta is caused by pathogenic variants in BMP1, CRTAP, FKBP10, LEPRE1, WNT1, PP1B, SERPINF1, SERPINH1, SP7, and TMEM38B. Bruck syndrome 2 is an autosomal recessive condition, and bone mineral density QTL18 due to pathogenic variants in PLS3 is an X-linked dominant condition.
Test Methods:
Using genomic DNA obtained from the submitted specimen, the coding exons and flanking splice junctions of the genes on this panel are enriched using a proprietary targeted capture method developed by GeneDx. These targeted regions are simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bidirectional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx). Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CHG analysis. Sequence and array CGH array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient’s clinical phenotype. Pathogenic variants in COL1A1 or COL1A2 are found in about 90% of cases of Osteogenesis imperfecta.4,5

The technical sensitivity of the sequencing test is estimated to greater than 99%. It will not detect deletions, insertions, or rearrangements greater than or equal to ten base pairs. The deletion/duplication testing can detect deletions or duplications encompassing one or more exons, including variants as small as 150-300 base pairs. Note that small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified.

Testing Options:

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<td>J797</td>
<td>Skeletal Dysplasia: Osteogenesis Imperfecta Panel</td>
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References:
1. Barkova, E et. al. (2014). Clinical Genetics, PMID: 24863959