PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Multiple Epiphyseal Dysplasia via *COL9A3* Gene Sequencing (Test #818)

Brief Description of Clinical Features: Multiple epiphyseal dysplasia is a clinically and genetically heterogeneous chondrodysplasia with either autosomal dominant or recessive inheritance. Dominant MED presents early in childhood, usually with pain in the hips and/or knees after exercise. Waddling gait may be present. Adult height is either in the lower range of normal or mildly shortened. The limbs are relatively short in comparison to the trunk. Pain and joint deformity can progress, resulting in early-onset osteoarthritis (Briggs et al. *GeneReviews* 2011).

Genetics: A number of genes are linked to autosomal dominant MED. Please refer to MED sequential gene test (Test #815) for more information. A minority of dominant MED is caused by mutations in the *COL9A3* gene, which encodes the alpha 3 chain of type IX collagen, a minor component of cartilaginous tissues. Type IX collagen is an integral component of cartilage and comprises three collagenous domains (COL1-COL3) separated by four non-collagenous domains (NC1-NC4) and is closely associated with type II collagen fibrils, where it is thought to act as a molecular bridge between collagen fibrils and other cartilage matrix components. All the reported mutations in *COL9A3* are splice site mutations, causing exon skipping in the COL3 domain, which may affect its ability to fold correctly or interact with other components of the cartilage extracellular matrix (Fresquet et al. *J Biol Chem* 282:34634–34643, 2007).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *COL9A3* gene plus ~50 bp of flanking non-coding DNA on each side. We will also sequence any single exon (Test #100, $190) in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: **Genomic: NC_000020.10** **mRNA: NM_001853.3**
Protein: NP_001844.3 **mRNA and Protein: CCDS 13505.1**

Indications for Test: Candidates for this test are patients with clinical features consistent with dominant MED but tested negative for other more commonly mutated MED genes, and family members of patients who have known *COL9A3* mutations.

Sensitivity of Test: Mutations in three type IX collagen genes (*COL9A1*, *COL9A2*, *COL9A3*) together account for probably ~10% of dominant MED cases (Briggs et al. *GeneReviews* 2011).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page four of the Requisition Form.

Prices: **Sequencing of *COL9A3* gene** **$ 1460**

CPT Codes:

Sample Ascertainment x1	83890 $ 30	DNA Isolation x1	83891 $ 40
Amplification x31	83898 $460	Sequencing x31	83904 $690
Separation x1	83894 $100	Interpretation/Report x1	83912 $140

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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