## Condition Description

Multiple epiphyseal dysplasia (MED; also known as epiphyseal dysplasia, multiple, EDM) is a group of skeletal disorders with heterogeneous genetic causes. MED has seven subtypes with a continuum of clinical severity among these types. Clinical and radiographic features continue to be used reliably to assign patients to this general disease category. Identification of the precise genetic defect is important, however, to permit carrier testing and early prenatal diagnosis. Molecular analysis is likely to expand the clinical spectrum of MED and may also provide data relevant to prognosis and future therapeutic intervention. The overall incidence of MED is estimated to be 1 in 10,000 births. Although the phenotype range is broad, MED is mainly characterized with short stature and early-onset osteoarthrosis. Radiographic findings for MED show a generalized abnormality of epiphyseal ossification without significant vertebral involvement. MED can be inherited in an autosomal dominant or autosomal recessive manner. The autosomal recessive form of MED includes features such as club foot and bilateral double-layered patellae.

### References:

- GeneReviews

## Genes

- COL2A1
- COL9A1
- COL9A2
- COL9A3
- COMP
- MATN3
- SLC26A2

## Indications

This test is indicated for individuals with:

- Short stature and early-onset osteoarthrosis.
- An abnormal radiographic findings show a generalized abnormality of epiphyseal ossification without significant vertebral involvement.

## Methodology

### Next Generation Sequencing:

In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Copy Number Analysis:

Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

## Detection

**Clinical Sensitivity:** 80%-90%. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory element pathogenic variants cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Analytical sensitivity for sequence variant detection is ~99%**.

### Copy Number Analysis:

The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

## Specimen Requirements

### Submit only 1 of the following specimen types

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**

- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated**

Specimen Requirements:
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:
- Oragene™ Saliva Collection Kit
- Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Special Instructions**

Radiographic results can help interpretation.

**Related Tests**

- Multiple Epiphyseal Dysplasia: Deletion/Duplication Panel