Osteogenesis Imperfecta
Indication-Specific Gene Panel

Including: sequencing and high resolution deletion/duplication analysis

PANEL DESCRIPTION:
Osteogenesis imperfecta (OI) is a genetic condition characterized by easily fractured bones. There are many subtypes that form a classification system. Osteogenesis imperfecta types I - IV are the most common; the remaining types are very rare. Overall, osteogenesis imperfecta has an incidence of 1 in every 10,000 individuals.1 This indication-specific panel is designed to detect both sequence-based mutations and small-scale deletions or duplications within 27 genes associated with various subtypes of osteogenesis imperfecta.

PANEL DETAILS:
- This panel includes both sequencing and high resolution deletion/duplication analysis of the genes specified.
  - Sequencing is performed using a customized next generation sequencing library. Analysis includes the coding exons of all genes in the panel plus ten bases into the introns and untranslated regions (5' and 3'). Sanger sequencing is performed to confirm variants suspected or confirmed to be pathogenic.
  - Deletion/duplication analysis is performed using a high resolution, custom microarray platform designed to target the genes of interest at the exon level.
- Detection rates are limited to the genes specified; this test does not provide whole genome analysis.
- Gene panels are a more cost-effective approach than single gene testing to confirm or establish a diagnosis. However, if single gene testing is desired for the patient or family members of an individual with a known mutation, that must be ordered separately.

RECOMMENDED TESTING STRATEGY:
Tests below can be ordered individually, however our laboratory’s recommended Comprehensive Testing for osteogenesis imperfecta includes the following two tests:

Next Generation Sequencing
- This gene test panel covers genes associated with osteogenesis imperfecta. Next generation sequencing (NGS) analyzes multiple genes at once, making this a cost-effective method of testing genes known to be as associated with this indication.

Targeted Deletion/Duplication Analysis
- If no pathogenic aberrations are detected by NGS, Deletion/Duplication Analysis is performed to identify partial or whole gene deletions and duplications in the associated genes.

DISORDERS INCLUDED IN THIS PANEL:
- Osteogenesis imperfecta subtypes I – XV
  - Type I: classic non-deforming OI with blue sclera [COL1A1, COL1A2, PLS3]
  - Type II: perinatally lethal OI [COL1A1, COL1A2]
  - Type III: progressively deforming OI [COL1A1, COL1A2]
  - Type IV: common variable OI with normal sclera [COL1A1, COL1A2]
  - Type V [IFITM5]
  - Type VI [SERPINF1]
  - Type VII - recessive [CRTAP]
  - Type VIII [P3H1 (previously LEPRE1)]
  - Type IX [PPIB]
  - Type X [SERPINH1]
- Type XI [FKBP10]
- Type XII [SP7]
- Type XIII [BMP1]
- Type XIV [TMEM388]
- Type XV [WNT1]
- Type XVI [CREB3L1] – all variants reported have been deletions
- Type XVII [SPARC]

- Bone mineral density QTL18 osteoporosis [PLS3]
- Bruck syndrome 2 (previously osteogenesis imperfecta with congenital joint contractures) [PLOD2]
- Familial hypophosphatemic rickets (General description of below)
  - Autosomal dominant hypophosphatemic rickets [FGF23]
  - Autosomal recessive hypophosphatemic rickets [DMP1, ENPP1]
  - Hypocalciuric hypercalcemia type I [CASR]
  - Hypophosphatemic rickets with hypercalciuria [SLC34A3]
  - X-linked dominant hypophosphatemic rickets [PHEX]
- Hypophosphatasia [ALPL]
- Osteoporosis pseudoglioma syndrome [LRP5]
- Cole Carpenter 1 syndrome [P4HB]
- Cole Carpenter 2 syndrome [SEC24D]

**INDICATIONS FOR TESTING:**
- Fractures
- Short or average stature
- Bone deformity
- Bowing of the limbs
- Radiographic findings: wormian bones, thin cortices, under-mineralization, codfish vertebrae, beaded ribs
- Blue/grey sclera hue
- Brittle teeth (dentinogenesis imperfecta)
- Hearing loss
- Loose joints and muscle weakness
- Triangular face
- Family history of OI
- Hypophosphatemia
- Bone pain
- Rickets
- Tooth Abscesses

**SPECIMEN COLLECTION & TRANSPORT:**
Complimentary test kits are available upon request, but are not required.

**SAMPLE TYPE and REQUIREMENTS:**
- **blood, > 3 months of age:** 3-5 ml whole blood in an EDTA tube (purple top)
- **blood, newborn:** 1-3 ml whole blood in an EDTA tube (purple top)
- **buccal swab:** 5 swabs
- **extracted DNA:** 5 µg in a DNA microcentrifuge tube

**SHIPPING:**
- Maintain and ship samples at room temperature.
- Coordinate transport for sample to be received in our laboratory within 24-48 hours of collection.
  - **LOCAL:** Call 402-559-5070 (option 1)
  - **OUT OF AREA:** Prior to shipment, please fax the completed test request form to 402-559-7248, including the FedEx® airbill tracking number.
- Saturday delivery MUST be checked when sending FedEx® on Friday.
- Please include Internal Billing Reference # 3155070600 on the FedEx® airbill.
- **Ship To:** Human Genetics Laboratory – Zip 5440
  UNMC Shipping & Receiving Dock
  601 S. Saddle Creek Road
  Omaha, NE 68106

**REQUIRED FORM:** The following form can be downloaded via our website.
- Postnatal Test Request Form

**OPTIONAL FORM:**
- Informed Consent for Genetic Testing

**POTENTIAL TEST RESULTS:**
Once a variant is confirmed, our laboratory team interprets this information in conjunction with the patient’s clinical findings and the scientific literature in order to classify a finding. There are three possible results:

- A **normal** result indicates that sequencing or deletion/duplication analysis of the genes analyzed did not find any pathogenic mutations or variants of uncertain clinical significance (or no clinically-significant chromosome anomalies were identified by microarray analysis).
- An **abnormal** (or **pathogenic**) result indicates that a pathogenic mutation was identified (or microarray analysis identified a genomic dosage anomaly [deletion or duplication] or ROH that likely provides an explanation for the individual’s clinical findings). Any available information regarding the phenotype associated with that mutation will accompany the technical details on the report.
- In some cases, the clinical significance of an identified sequence variant (or chromosomal anomaly detected by microarray) may not be well understood. These variants (anomalies) will be reported as **variants of uncertain clinical significance (UCS)**. Any available information about the molecular characteristics of the genetic change and the relationship of the genetic change to phenotype will be included on the report. Over time, as more patients are reported, a variant of uncertain clinical significance may be revised to an informative result, and a revised report will be generated.
- Parental testing may be recommended in order to classify the result as **de novo** or familial for the purpose of recurrence risk calculation.

**TURN-AROUND TIMES:** For all sample types, results are typically available in 2-6 weeks.

**BILLING:** Our laboratory offers patient/self-pay, insurance (including Medicare/Medicaid), and client/institution billing options. Verifying coverage requirements or obtaining preauthorization PRIOR TO OR AT THE TIME OF SPECIMEN COLLECTION is often necessary. We provide preauthorization services upon request by calling 402-559-5070 (option 3); the following form is helpful for obtaining the information required by insurance providers and can be downloaded via our website.
- Request for Insurance Preauthorization

In some circumstances, a test may be warranted even though insurance coverage is denied or not guaranteed. For these situations, we request the following form be signed by the patient and submitted with the sample. This helps inform patients of their potential financial responsibility, should the costs of genetic testing not be paid by their insurance provider.
- Advanced Beneficiary Notice of Noncoverage (ABN) – required when billing Medicare

**CPT CODES:**
- **Next Generation Sequencing:** 81407(x2)
- **Targeted Deletion/Duplication Analysis:** 81228

**PRICING:** For current costs contact the laboratory billing staff at 402-559-5070 (option 3).
**GENE LIST:** (expanded panel, version 3_27)

This 27 gene panel is applied to all testing performed on and after April 1, 2016.

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* Previously known as LEPRE1

**REFERENCES:**

updated 4/2016