Test Definition: OIBFG

Osteogenesis Imperfecta and Bone Fragility Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive osteogenesis imperfecta and other hereditary conditions associated with bone fragility

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 25 genes associated with osteogenesis imperfecta (OI) and other hereditary conditions associated with bone fragility: *ALPL, ANO5, BMP1, COL1A1, COL1A2, CREB3L1, CRTAP, FKBP10, IFITM5, LRP5, MBTPS2, P3H1, P4HB, PLOD2, PLS3, PPIB, SEC24D, SERPINF1, SERPINH1, SP7, SPARC, TAPT1, TMEM38B, WNT1,* and *XYLT2*. See Targeted Genes and Methodology Details for Osteogenesis Imperfecta and Bone Fragility Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for OI and other hereditary conditions associated with bone fragility.

Prior Authorization is available for this assay.

Testing Algorithm

For prenatal specimens only:

-If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture will be added at an additional charge.
-If chorionic villus specimen (nonconfluent cultured cells) is received, fibroblast culture will be added at an additional charge.

For any prenatal specimen that is received, maternal cell contamination testing will be performed at an additional charge.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
- Targeted Genes and Methodology Details for Osteogenesis Imperfecta and Bone Fragility Gene Panel
- Osteogenesis Imperfecta and Bone Fragility Gene Panel (OIBFG) Prior Authorization Ordering Instructions

Method Name
Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH/ Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Additional Testing Requirements
All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen as **this must be a different order number than the prenatal specimen**.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Necessary Information
Prior Authorization is available, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

Prenatal Specimens
Due to its complexity, consultation with the laboratory is required for all prenatal testing; call 800-533-1710 to speak to a genetic counselor.

Specimen Type: Amniotic fluid
Container/Tube: Amniotic fluid container
Specimen Volume: 20 mL
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional information:
1. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid.
2. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Chorionic villi
Container/Tube: 15-mL tube containing 15 mL of transport media
Specimen Volume: 20 mg
Specimen Stability Information: Refrigerated
Additional Information:
1. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Molecular Testing, Chorionic Villi/Products of Conception.
2. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Acceptable:
Specimen Type: Confluent cultured cells
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured cells from another laboratory.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Additional Information: All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
3. Osteogenesis Imperfecta and Bone Fragility Gene Panel (OIBFG) Prior Authorization Ordering Instructions
4. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

Specimen Minimum Volume

Blood: 1 mL; Other specimen types: See Specimen Required

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Osteogenesis imperfecta (OI) is a hereditary skeletal dysplasia syndrome characterized primarily by bone fragility and skeletal deformities, with other possible features including dental abnormalities, hearing loss, and blue/gray sclera.(1,2) Historically, OI was classified into subtypes based on clinical presentation only: nondeforming with persistently blue sclera (OI type I), perinatal lethal (OI type II), progressively deforming (OI type III), moderate (OI type IV), and with calcification of the interosseous membranes and/or hypertrophic callus (OI type V). While these clinical classifications are still commonly used, it is recommended that OI subtypes are classified by genetic etiology.(3) Currently, there are approximately 20 different genetic subtypes of OI with variable modes of inheritance and pathophysiology.(1-3)

The most common genetic etiology of OI is disease-causing variants in the *COL1A1* and *COL1A2* genes encoding the pro alpha 1(I) and pro alpha 2(I) chains of type I procollagen, respectively. It is estimated that up to 25% of cases of OI are caused by disease-causing variants in either *COL1A1* or *COL1A2*.(1-3) Disease-causing variants in these genes result in the inability to properly synthesize the pro alpha 1/2 molecules ultimately leading to abnormal or absent collagen I, a critical molecule for the structural integrity of bone. *COL1A1/2*-associated OI is inherited in an autosomal dominant manner and can result in a spectrum of disease severity, classified into OI types I-IV.(3)

Other genetic etiologies of OI are associated with genes involved in bone mineralization, collagen modification, collagen processing, collagen cross-linking, and osteoblast differentiation and function.(3) The majority of these less common genetic OI subtypes are inherited in an autosomal recessive manner, with the exception of autosomal dominant *IFITM5*-associated OI (also known as OI type V), and X-linked recessive *MBTPS2*-associated OI (also known as OI type XVII).

Several genetic conditions leading to bone fragility have significant overlap with OI. Additional conditions covered by this panel include *ALPL*-associated hypophosphatasia, *ANO5*-associated gnathodiaphyseal dysplasia, *FKBP10*-associated Bruck syndrome, *LRP5*-associated osteoporosis, *P4HB*-associated Cole-Carpenter syndrome, *PLOD2*-associated Bruck syndrome, *PLS3*-associated X-linked osteoporosis, *TAPT1*-associated osteochondrodysplasia, and *XYLT2*-associated spondyloocular syndrome with bone fragility, cataracts and hearing defects.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variants in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the Targeted Genes and Methodology Details for Osteogenesis Imperfecta and Bone Fragility Gene Panel for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(4) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Marom R, Rabenhorst BM, Morello R: Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol. 2020 Oct;183(4):R95-R106. doi:10.1530/EJE-20-0299
2. Steiner RD, Basel D: COL1A1/2 osteogenesis imperfecta. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated May 6, 2021. Accessed August 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1295/
3. Marini JC, Forlino A, Bachinger HP, et al: Osteogenesis imperfecta. Nat Rev Dis Primers. 2017 Aug 18;3:17052. doi: 10.1038/nrdp.2017.52
4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Osteogenesis Imperfecta and Bone Fragility Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ALPL, ANO5, BMP1, COL1A1, COL1A2, CREB3L1, CRTAP, FKBP10, IFITM5, LRP5, MBTPS2, P3H1, P4HB, PLOD2, PLS3, PPIB, SEC24D, SERPINF1, SERPINH1, SP7, SPARC, TAPT1, TMEM38B, WNT1,* and *XYLT2*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cord blood, amniotic fluid, cultured amniocytes, chorionic villi, cultured chorionic villi: 1 month

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81406 x2
81408 x2
81479
81479 (if appropriate for government payers)

Prior Auhtorization

Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
OIBFG	OI and Bone Fragility Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
617408	Test Description	62364-5
617409	Specimen	31208-2
617410	Source	31208-2
617411	Result Summary	50397-9
617412	Result	82939-0
617413	Interpretation	69047-9

617414	Additional Results	82939-0
617415	Resources	99622-3
617416	Additional Information	48767-8
617417	Method	85069-3
617418	Genes Analyzed	48018-6
617419	Disclaimer	62364-5
617420	Released By	18771-6