Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	6/18/1962
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing

ARUP test code 3001607

Osteogenesis Imperfecta Specimen	Whole Blood
Osteogenesis Imperfecta Interp	Positive

RESULT
One pathogenic variant was detected in the COL1A1 gene. One variant of uncertain significance was detected in the SLC34A3 gene.

PATHOGENIC VARIANT
Gene: COL1A1 (NM_000088.4)
Nucleic Acid Change: c.3421C>T; Heterozygous
Amino Acid Alteration: p.Arg1141Ter
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: SLC34A3 (NM_080877.2)
Nucleic Acid Change: c.544C>T; Heterozygous
Amino Acid Alteration: p.Arg182Trp
Inheritance: Autosomal recessive

INTERPRETATION
One pathogenic variant, c.3421C>T; p.Arg1141Ter, was detected in the COL1A1 gene by massively parallel sequencing. Pathogenic germline COL1A1 variants are inherited in an autosomal dominant manner, and are associated with both skeletal and/or aortopathy disorders including: osteogenesis imperfecta type I (MIM: 166200), osteogenesis imperfecta type II (MIM: 166210), osteogenesis imperfecta type III (MIM: 259420), osteogenesis imperfecta type IV (MIM: 166220), arthrochalasia type Ehlers-Danlos syndrome 1 (MIM: 130060) and combined osteogenesis imperfecta and Ehlers-Danlos syndrome 1 (MIM: 619115). This result is consistent with a diagnosis of a COL1A1-related disorder. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

One variant of uncertain clinical significance, c.544C>T; p.Arg182Trp, was detected in the SLC34A3 gene by massively parallel sequencing. Pathogenic variants in SLC34A3 are associated with autosomal recessive hypophosphatemic rickets with hypercalciuria (MIM: 241530). However, it is uncertain whether this variant is disease-associated or benign.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The COL1A1 c.3421C>T; p.Arg1141Ter variant (rs72656314) is

H=High, L=Low, *=Abnormal, C=Critical

reported in the literature in individuals affected with osteogenesis imperfecta (Balasubramanian 2016, Bardai 2017, Chen 2022, Higuchi 1994, Mei 2022, Tuysuz 2022, Willing 1994). This variant is also reported in ClinVar (Variation ID: 17337), but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

The SLC34A3 c.544C>T; p.Arg182Trp variant (rs199747826) is reported in the literature in the compound heterozygous state with a different pathogenic SLC34A3 variant in an individual affected with hypophosphatemic rickets with hypercalciuria (Tencza 2009). This variant is also reported in ClinVar (Variation ID: 1438804), and is found in the general population with an overall allele frequency of 0.0016% (4/248476 alleles) in the Genome Aggregation Database. Computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.244). However, given the lack of clinical and functional data, the significance of this variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended. At-risk family members should be offered testing for the identified pathogenic COL1A1 variant (Familial Targeted Sequencing, ARUP test code 3005867). Surveillance of the literature for new information concerning the uncertain variant is recommended.

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES
Balasubramanian M et al. Osteogenesis imperfecta: Ultrastructural and histological findings on examination of skin revealing novel insights into genotype-phenotype correlation. Ultrastruct Pathol. 2016;40(2):71-6. PMID: 26863094.
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Higuchi Y et al. Genetic analysis in Japanese patients with osteogenesis imperfecta: Genotype and phenotype spectra in 96 probands. Mol Genet Genomic Med. 2021 Jun;9(6):e1675. PMID: 33939306.
Mei Y et al. Comparing Clinical and Genetic Characteristics of De Novo and Inherited COL1A1/COL1A2 Variants in a Large Chinese Cohort of Osteogenesis Imperfecta. Front Endocrinol (Lausanne). 2022 Jul 14;13:935905. PMID: 35909573.
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Tuysuz B et al. Osteogenesis imperfecta in 140 Turkish families: Molecular spectrum and, comparison of long-term clinical outcome of those with COL1A1/A2 and biallelic variants. Bone. 2022 Feb;155:116293. PMID: 34902613.
Willing MC et al. Osteogenesis imperfecta type I: molecular heterogeneity for COL1A1 null alleles of type I collagen. Am J Hum Genet. 1994 Oct;55(4):638-47. PMID: 7942841.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Osteogenesis Imperfecta and Low Bone Density Panel, Sequencing

CHARACTERISTICS: Although osteoporosis is present in 10 percent of the US population, monogenetic causes of osteoporosis, such as osteogenesis imperfecta (OI), are rare. OI is defined by a continuum of phenotypes ranging from individuals with perinatal lethal OI, severe skeletal deformities, dentinogenesis imperfecta (DI) and severe short stature to individuals with normal stature, dentition and lifespan but mild predisposition to fractures. This panel targets monogenic forms of OI and low bone density; it excludes genes causative for hypophosphatemic rickets and osteopetrosis.
EPIDEMIOLOGY: 6 to 7 per 100,000 for OI.
CAUSE: Varies depending on causative gene; pathogenic germline variants in COL1A1 and COL1A2 are causative for 90 percent of OI.

INHERITANCE: Varies depending on causative gene; autosomal dominant for COL1A1 and COL1A2.

CLINICAL SENSITIVITY: Greater than 90 percent for OI and unknown for other monogenic causes of low bone density.

GENES TESTED: ALPL, ANO5, BMP1, CASR, CLCN5, COL1A1, COL1A2, CREB3L1, CRTAP, CYP27B1, FKBP10, GORAB, IFITM5, LRP5*, P3H1, P4HB, PLOD2, PLS3, PPIB, SEC24D, SERPINF1, SERPINH1, SLC34A3, SP7, SPARC, TMEM38B, WNT1.

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a monogenic form of OI or low bone density. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants, large deletions/duplications/inversions and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following region is not sequenced due to technical limitations of the assay:
LRP5 (NM_002335) exon 1

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was

performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Osteogenesis Imperfecta Specimen	23-277-401823	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Osteogenesis Imperfecta Interp	23-277-401823	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical