BSC_CON_2.26	Genetic Testing: Skeletal Dysplasia and Rare Bone Disorders		
Original Policy Date:	December 1, 2023	**Effective Date:**	January 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 13

Example Test Table

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Osteogenesis Imperfecta	Osteogenesis imperfecta COL1A1 & COL1A2 NGS Panel (HNL Genomics)	81406, 81408, 81479
	Osteogenesis Imperfecta Panel (PreventionGenetics, part of Exact Sciences)	
	Osteogenesis Imperfecta NGS Panel - Dominant & Recessive (HNL Genomics)	
Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder	Skeletal Disorders Panel (Invitae)	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479
	Skeletal Dysplasia Core & Extended NGS Panel (HNL Genomics)	
	Comprehensive Skeletal Dysplasias and Disorders Panel (Blueprint Genetics)	
Other Covered Skeletal Dysplasias and Rare Bone Disorders		
Other Covered Skeletal Dysplasias and Rare Bone Disorders	varies	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479

Policy Statement

OSTEOGENESIS IMPERFECTA

I. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81406, 81408, 81479) that includes *COL1A1* and *COL1A2* to establish or confirm a diagnosis of osteogenesis imperfecta (OI) may be considered **medically necessary** when:
   A. The member has **any** of the following:
      1. Fractures with minimal or no trauma in the absence of other factors, such as non-accidental trauma (NAT) or other known disorders of bone, **OR**
      2. Short stature, often with bone deformity, **OR**

3. Blue/gray scleral hue, **OR**
4. Dentinogenesis imperfecta (DI), **OR**
5. Progressive, postpubertal hearing loss, **OR**
6. Ligamentous laxity or other signs of connective tissue abnormality, **OR**
7. Family history of OI, **OR**
8. Fractures of varying ages and stages of healing (often of the long bones), **OR**
9. "Codfish" vertebrae, **OR**
10. Wormian bones, **OR**
11. Protrusio acetabuli, **OR**
12. Low bone mass or osteoporosis.

II. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81406, 81408, 81479) that includes *COL1A1* and *COL1A2* to establish or confirm a diagnosis of osteogenesis imperfecta is considered **investigational** for all other indications.

MULTIGENE PANEL ANALYSIS FOR SKELETAL DYSPLASIA OR RARE BONE DISORDER

III. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a post-natal diagnosis of a skeletal dysplasia or a rare bone disorder may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The differential diagnosis includes more than one type of skeletal dysplasia or bone disorder, **AND**
   B. The member displays **one or more** of the following clinical features of a skeletal dysplasia:
      1. Prenatal ultrasound that showed shortening of the bones of the arms and legs more than 3 standard deviations below the mean, **OR**
      2. Prenatal ultrasound that showed head circumference greater than 75th percentile, **OR**
      3. Prenatal ultrasound that showed bone irregularities (e.g., bowed, fractured, thickened, thin, undermineralized, etc.), **OR**
      4. Prenatal ultrasound that showed abnormal ribs or a small chest circumference, **OR**
      5. Postnatal short stature with height or length less than 3rd percentile

IV. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder is considered **investigational** for all other indications.

OTHER COVERED SKELETAL DYSPLASIA AND RARE BONE DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

V. Genetic testing to establish or confirm one of the following skeletal dysplasias or rare bone disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see VI below):
   A. Achondroplasia Group
      1. Achondroplasia
      2. Hypochondroplasia
      3. Thanatophoric Dysplasia
   B. Type II Collagenopathies
      1. Hypochondrogenesis
      2. Spondyloepiphyseal Dysplasia
   C. Type XI Collagen Disorders
      1. Fibrochondrogenesis

2. Otospondylomegaepiphyseal Dysplasia (OSMED)

D. Sulfation Disorders
   1. Achondrogenesis IB
   2. Atelosteogenesis II
   3. Diastrophic Dysplasia
   4. Chondrodysplasia with Congenital Joint Dislocations

E. Filamin Disorders and Similar Disorders
   1. Atelosteogenesis Type I
   2. Atelosteogenesis Type III
   3. Larsen Syndrome
   4. Spondylo-Carpal-Tarsal Dysplasia

F. Short-Rib Dysplasias (with and without Polydactyly)
   1. Chondroectodermal Dysplasia (Ellis-van Creveld (EVC))
   2. Short-Rib Polydactyly Syndrome I, II, III, IV including Asphyxiating Thoracic Dystrophy

G. Metaphyseal Dysplasias
   1. Cartilage-Hair Hypoplasia

H. Spondylo-Epi-(Meta)-Physeal Dysplasia
   1. SEMD, Short Limb Abnormal Calcification Type

I. Acromesomelic Disorders
   1. Acromesomelic Dysplasia, Type Maroteaux

J. Mesomelic and Rhizo-Mesomelic Dysplasias
   1. Langer Type (Homozygous Dyschondrosteosis)

K. Bent Bone Dysplasias
   1. Campomelic Dysplasia
   2. Stuve-Wiedemann Dysplasia
   3. Bent Bone Dysplasia FGFR2 Type

L. Slender Bone Dysplasia
   1. Microcephalic Osteodysplastic Primordial Dwarfism
   2. Osteocraniostenosis

M. Neonatal Osteosclerotic Dysplasias
   1. Bloomstrand Dysplasia
   2. Caffey Disease (Infantile)
   3. Raine Dysplasia

N. Increased Bone Density Group
   1. Osteopetrosis

O. Abnormal Mineralization Group
   1. Hypophosphatasia

P. Multiple Epiphyseal Dysplasia and Pseudoachondroplasia Group
   1. Multiple Epiphyseal Dysplasia (MED) - Autosomal Dominant
   2. Multiple Epiphyseal Dysplasia (MED) - Autosomal Recessive
   3. Stickler Syndrome

Q. Hereditary Multiple Osteochondromas

VI. Genetic testing to establish or confirm the diagnosis of all other skeletal dysplasias or rare bone disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly sources.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

DEFINITIONS
Non-accidental Trauma (NAT) refers to injury that is purposely inflicted upon a child (e.g., child abuse). NAT often occurs as injury to the skin and soft tissue, but approximately a third of NATs are fractures.

Coding
See the Codes table for details.

Description

Skeletal dysplasias are a category of rare genetic disorders that affect bones and joints and are estimated to affect 2.4 per 10,000 births, and some forms of skeletal dysplasia can be suspected based on prenatal ultrasound. There are more than 350 distinct skeletal disorders that have been described, and some skeletal dysplasias can be lethal, often due to a significantly small rib cage that restricts lung development. The osteogenesis imperfecta group of disorders are sometimes classified as skeletal dysplasias, while other times they are considered bone fragility disorders.

Genetic testing has allowed for gene identification in more than two thirds of the skeletal dysplasias. Testing allows for more precise diagnosis facilitating health care providers' care based on the established natural history of the individual disorder. For some skeletal dysplasias, knowing the specific disease causing variant or variants can impart prognostic information. A few skeletal dysplasias are currently amenable to pharmacologic therapy, though such therapies may be reserved for patients with confirmed genetic diagnosis. The familial recurrence risk and long term natural history differs based on the underlying genetic basis of disease.

Per GeneReviews*, osteogenesis imperfecta (OI) should be distinguished from child physical abuse/non-accidental trauma (NAT). The prevalence of physical abuse is much greater than the prevalence of OI, and on rare occasions, the two can be present concurrently. Patient history, family history, physical examination, radiographic imaging, fracture investigation, and the clinical course all contribute to distinguishing OI from NAT. The overlap in clinical features includes multiple or recurrent fractures, fractures that do not match the history of trauma, and the finding of fractures of varying ages and at different stages of healing. Rib fractures are much more common in NAT than in osteogenesis imperfecta.

*GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Related Policies

This policy document provides coverage criteria for Genetic Testing for Skeletal Dysplasia and Rare Bone Disorders. Please refer to:

- ***Genetic Testing: Aortopathies and Connective Tissue Disorders*** for coverage criteria related to Ehlers-Danlos syndrome and other connective tissue disorders.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic testing for disorders that affect multiple systems.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to skeletal dysplasias and rare bone disorders that is not specifically discussed in this or another non-general policy, including known familial variant testing.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background
Osteogenesis Imperfecta

GeneReviews: COL1A1/2 Osteogenesis Imperfecta
GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

The recommended diagnostic testing for osteogenesis imperfecta is as follows:

COL1A1/2 osteogenesis imperfecta (OI) should be suspected in individuals with the following clinical, radiographic, and laboratory features.

- Fractures with minimal or no trauma in the absence of other factors, such as non-accidental trauma (NAT) or other known disorders of bone
- Short stature or stature shorter than predicted based on stature of unaffected family members, often with bone deformity
- Blue/gray scleral hue
- Dentinogenesis imperfecta (DI)
- Progressive, postpubertal hearing loss
- Ligamentous laxity and other signs of connective tissue abnormality
- Family history of OI, usually consistent with autosomal dominant inheritance

Radiographic features of OI change with age. The major findings include the following:

- Fractures of varying ages and stages of healing, often of the long bones but may also rarely involve ribs and skull. Metaphyseal fractures can be seen in a very small number of children with OI. Rib fractures are much more common in NAT than in OI.
- "Codfish" vertebrae, which are the consequence of spinal compression fractures, seen more commonly in adults.
- Wormian bones, defined as "sutural bones which are 6 mm by 4 mm (in diameter) or larger, in excess of ten in number, with a tendency to arrange in a mosaic pattern." Wormian bones are suggestive of but not pathognomonic for OI.
- Protrusio acetabuli, in which the socket of the hip joint is too deep and the acetabulum bulges into the cavity of the pelvis causing intrapelvic protrusion of the acetabulum.
- Low bone mass or osteoporosis detected by dual energy x-ray absorptiometry (DEXA). Bone density can be normal, especially in individuals with OI type I, as DEXA measures mineral content rather than collagen.

"A multigene panel that includes *COL1A1*, *COL1A2*, and other genes of interest is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and variants in genes that do not explain the underlying phenotype."

Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder

Krakow et al 2009

A guideline for prenatal diagnosis of fetal skeletal dysplasias (Krakow, Lachman, Rimoin, 2009) recommends the follow criteria:

- Fetuses with long bone measurements at or less than the 5th centile or greater than 3 SD below the mean should be evaluated in a center with expertise in the recognition of skeletal dysplasias. If the patient cannot travel, arrangements may be able to be made for evaluation of ultrasound videotapes or hard copy images.
- The following fetal ultrasound measurements should be visualized and plotted against normative values: fetal cranium (biparietal diameter and head circumference), facial profile, mandible, clavicle, scapula, chest circumference, vertebral bodies, all fetal long bones, and the hands and feet. Fetuses with long bone parameters more than 3 SD below the mean should be strongly suspected of having a skeletal dysplasia, especially if the head circumference is greater than the 75th centile
- Lethality should be determined by chest circumference to abdominal circumference ratio and/or femur length to abdominal circumference measurement ratio. A chest-to abdominal circumference ratio of less than 0.6 or femur length to abdominal circumference ratio of 0.16 strongly suggests a perinatal lethal disorder, although there are exceptions. The findings should be conveyed to the physicians caring for the patient and to the patient. (p. 5)

In addition, close attention should be paid to the shape and mineralization pattern of the fetal calvarium and fetal skeleton (poor or ectopic mineralization). Determining the elements of the skeleton that are abnormal, coupled with the findings of mineralization and shape of the bones can aid in diagnosis. (p. 3)

American College of Medical Genetics and Genomics (ACMG)

For diagnosis of genetic causes of short stature, the American College of Medical Genetics clinical practice resource for evaluation of short stature (Seaver et al, 2009) is as follows:

> "The definition most commonly used for short stature is height-for-age less than two standard deviations below average for gender, which is demonstrated on the standard growth curves as a length or height less than the 3rd centile." (p. 466)

Scocchia, et al.

A 2021 study of the clinical utility of multigene panel testing for an unselected population of individuals with suspected skeletal dysplasia demonstrated a high diagnostic yield in individuals with a suspected skeletal dysplasia or growth disorder. (p. 1)

A molecular diagnosis was established in 42% of patients (228/543). Diagnostic variants were identified in 71 genes, with variation in nearly half of these genes contributing to a molecular diagnosis for a single patient in this cohort. Overall, the most common genes in which molecular diagnoses were identified included: *COL2A1* associated with type II collagenopathies; *FGFR3* associated with achondroplasia, thanatophoric dysplasia, hypochondroplasia, and other conditions such as FGFR-related craniosynostoses; and *COL1A1* or *COL1A2*, associated with osteogenesis imperfecta. Together, these four genes accounted for over one third of all molecular diagnoses across the cohort. (p. 2-3)

Other Covered Skeletal Dysplasia and Rare Bone Disorders

International Skeletal Dysplasia Society

The International Skeletal Dysplasia Society published an updated categorization of skeletal dysplasias (Unger, 2023):

> "The 'Nosology of genetic skeletal disorders' has undergone its 11th revision and now contains 771 entries associated with 552 genes reflecting advances in molecular delineation of new disorders thanks to advances in DNA sequencing technology….As with the previous versions,

the list of disorders and genes in the Nosology may be useful in considering the differential diagnosis in the clinic, directing bioinformatic analysis of next-generation sequencing results, and provide a basis for novel advances in biology and medicine." (p. 1165)

References

1. Seaver LH, Irons M; American College of Medical Genetics (ACMG) Professional Practice and Guidelines Committee. ACMG practice guideline: genetic evaluation of short stature [published correction appears in Genet Med. 2009 Oct;11(10):765]. Genet Med. 2009;11(6):465-470. doi:10.1097/GIM.0b013e3181a7e8f8
2. Unger S, Ferreira CR, Mortier GR, et al. Nosology of Genetic Skeletal Disorders: 2023 revision. American J of Med Genetics Pt A. 2023;191(5):1164-1209.
3. Steiner RD, Basel D. COL1A1/2 Osteogenesis Imperfecta. 2005 Jan 28 [Updated 2024 Mar 14]. In: Adam MP, Mirzaa GM Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1295/
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5. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
6. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/
7. Scocchia, A., Kangas-Kontio, T., Irving, M. *et al.* Diagnostic utility of next-generation sequencing-based panel testing in 543 patients with suspected skeletal dysplasia. *Orphanet J Rare Dis* 16, 412 (2021). https://doi.org/10.1186/s13023-021-02025-7
8. Krakow D, Lachman RS, Rimoin DL. Guidelines for the prenatal diagnosis of fetal skeletal dysplasias. Genet Med. 2009;11(2):127-133. doi:10.1097/GIM.0b013e3181971ccb

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/01/2023	New policy.
12/01/2024	Annual review. No change to policy statement.
01/01/2025	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Genetic Testing: Skeletal Dysplasia and Rare Bone Disorders **BSC_CON_2.26** **Policy Statement:** **OSTEOGENESIS IMPERFECTA** I. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81406, 81408, 81479) that includes *COL1A1* and *COL1A2* to establish or confirm a diagnosis of osteogenesis imperfecta (OI) may be considered **medically necessary** when: A. The member has **any** of the following: 1. Fractures with minimal or no trauma in the absence of other factors, such as non-accidental trauma (NAT) or other known disorders of bone 2. Short stature, often with bone deformity 3. Blue/gray scleral hue 4. Dentinogenesis imperfecta (DI) 5. Progressive, postpubertal hearing loss 6. Ligamentous laxity or other signs of connective tissue abnormality 7. Family history of OI, typically with autosomal dominant inheritance 8. Fractures of varying ages and stages of healing (often of the long bones) 9. "Codfish" vertebrae 10. Wormian bones 11. Protrusio acetabuli 12. Low bone mass or osteoporosis. II. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81406, 81408, 81479) for osteogenesis imperfecta is considered **investigational** for all other indications.	**Genetic Testing: Skeletal Dysplasia and Rare Bone Disorders** **BSC_CON_2.26** **Policy Statement:** **OSTEOGENESIS IMPERFECTA** I. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81406, 81408, 81479) that includes *COL1A1* and *COL1A2* to establish or confirm a diagnosis of osteogenesis imperfecta (OI) may be considered **medically necessary** when: A. The member has **any** of the following: 1. Fractures with minimal or no trauma in the absence of other factors, such as non-accidental trauma (NAT) or other known disorders of bone, **OR** 2. Short stature, often with bone deformity, **OR** 3. Blue/gray scleral hue, **OR** 4. Dentinogenesis imperfecta (DI), **OR** 5. Progressive, postpubertal hearing loss, **OR** 6. Ligamentous laxity or other signs of connective tissue abnormality, **OR** 7. Family history of OI, **OR** 8. Fractures of varying ages and stages of healing (often of the long bones), **OR** 9. "Codfish" vertebrae, **OR** 10. Wormian bones, **OR** 11. Protrusio acetabuli, **OR** 12. Low bone mass or osteoporosis. II. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81406, 81408, 81479) that includes *COL1A1* and *COL1A2* to establish or confirm a diagnosis of osteogenesis imperfecta is considered **investigational** for all other indications.

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
MULTIGENE PANEL ANALYSIS FOR SKELETAL DYSPLASIA OR RARE BONE DISORDER III. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a post-natal diagnosis of a skeletal dysplasia or a rare bone disorder may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member displays **one or more** of the following clinical features of a skeletal dysplasia: 1. Prenatal ultrasound that showed shortening of the bones of the arms and legs more than 3 standard deviations below the mean 2. Prenatal ultrasound that showed head circumference greater than 75th percentile 3. Prenatal ultrasound that showed bone irregularities (e.g., bowed, fractured, thickened, thin, undermineralized, etc.) 4. Prenatal ultrasound that showed abnormal ribs or a small chest circumference 5. Postnatal short stature with height or length less than 3rd percentile B. The differential diagnosis includes more than one type of skeletal dysplasia or bone disorder. IV. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder is considered **investigational** for all other indications.	**MULTIGENE PANEL ANALYSIS FOR SKELETAL DYSPLASIA OR RARE BONE DISORDER** III. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a post-natal diagnosis of a skeletal dysplasia or a rare bone disorder may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The differential diagnosis includes more than one type of skeletal dysplasia or bone disorder, **AND** B. The member displays **one or more** of the following clinical features of a skeletal dysplasia: 1. Prenatal ultrasound that showed shortening of the bones of the arms and legs more than 3 standard deviations below the mean, **OR** 2. Prenatal ultrasound that showed head circumference greater than 75th percentile, **OR** 3. Prenatal ultrasound that showed bone irregularities (e.g., bowed, fractured, thickened, thin, undermineralized, etc.), **OR** 4. Prenatal ultrasound that showed abnormal ribs or a small chest circumference, **OR** 5. Postnatal short stature with height or length less than 3rd percentile IV. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder is considered **investigational** for all other indications.
OTHER COVERED SKELETAL DYSPLASIA AND RARE BONE DISORDERS The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.	**OTHER COVERED SKELETAL DYSPLASIA AND RARE BONE DISORDERS** The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
V. Genetic testing to establish or confirm one of the following skeletal dysplasias or rare bone disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see VI below): A. Achondroplasia Group 1. Achondroplasia 2. Hypochondroplasia 3. Thanatophoric Dysplasia B. Type II Collagenopathies 1. Hypochondrogenesis 2. Spondyloepiphyseal Dysplasia C. Type XI Collagen Disorders 1. Fibrochondrogenesis 2. Otospondylomegaepiphyseal Dysplasia (OSMED) D. Sulfation Disorders 1. Achondrogenesis IB 2. Atelosteogenesis II 3. Diastrophic Dysplasia 4. Chondrodysplasia with Congenital Joint Dislocations E. Filamin Disorders and Similar Disorders 1. Atelosteogenesis Type I 2. Atelosteogenesis Type III 3. Larsen Syndrome 4. Spondylo-Carpal-Tarsal Dysplasia F. Short-Rib Dysplasias (with and without Polydactyly) 1. Chondroectodermal Dysplasia (Ellis-van Creveld (EVC)) 2. Short-Rib Polydactyly Syndrome I, II, III, IV including Asphyxiating Thoracic Dystrophy G. Metaphyseal Dysplasias 1. Cartilage-Hair Hypoplasia H. Spondylo-Epi-(Meta)-Physeal Dysplasia 1. SEMD, Short Limb Abnormal Calcification Type I. Acromesomelic Disorders 1. Acromesomelic Dysplasia, Type Maroteaux	V. Genetic testing to establish or confirm one of the following skeletal dysplasias or rare bone disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see VI below): A. Achondroplasia Group 1. Achondroplasia 2. Hypochondroplasia 3. Thanatophoric Dysplasia B. Type II Collagenopathies 1. Hypochondrogenesis 2. Spondyloepiphyseal Dysplasia C. Type XI Collagen Disorders 1. Fibrochondrogenesis 2. Otospondylomegaepiphyseal Dysplasia (OSMED) D. Sulfation Disorders 1. Achondrogenesis IB 2. Atelosteogenesis II 3. Diastrophic Dysplasia 4. Chondrodysplasia with Congenital Joint Dislocations E. Filamin Disorders and Similar Disorders 1. Atelosteogenesis Type I 2. Atelosteogenesis Type III 3. Larsen Syndrome 4. Spondylo-Carpal-Tarsal Dysplasia F. Short-Rib Dysplasias (with and without Polydactyly) 1. Chondroectodermal Dysplasia (Ellis-van Creveld (EVC)) 2. Short-Rib Polydactyly Syndrome I, II, III, IV including Asphyxiating Thoracic Dystrophy G. Metaphyseal Dysplasias 1. Cartilage-Hair Hypoplasia H. Spondylo-Epi-(Meta)-Physeal Dysplasia 1. SEMD, Short Limb Abnormal Calcification Type I. Acromesomelic Disorders 1. Acromesomelic Dysplasia, Type Maroteaux

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J. Mesomelic and Rhizo-Mesomelic Dysplasias 1. Langer Type (Homozygous Dyschondrosteosis) K. Bent Bone Dysplasias 1. Campomelic Dysplasia 2. Stuve-Wiedemann Dysplasia 3. Bent Bone Dysplasia FGFR2 Type L. Slender Bone Dysplasia 1. Microcephalic Osteodysplastic Primordial Dwarfism 2. Osteocraniostenosis M. Neonatal Osteosclerotic Dysplasias 1. Bloomstrand Dysplasia 2. Caffey Disease (Infantile) 3. Raine Dysplasia N. Increased Bone Density Group 1. Osteopetrosis O. Abnormal Mineralization Group 1. Hypophosphatasia P. Multiple Epiphyseal Dysplasia and Pseudoachondroplasia Group 1. Multiple Epiphyseal Dysplasia (MED) - Autosomal Dominant 2. Multiple Epiphyseal Dysplasia (MED) - Autosomal Recessive 3. Stickler Syndrome Q. Hereditary Multiple Osteochondromas	J. Mesomelic and Rhizo-Mesomelic Dysplasias 1. Langer Type (Homozygous Dyschondrosteosis) K. Bent Bone Dysplasias 1. Campomelic Dysplasia 2. Stuve-Wiedemann Dysplasia 3. Bent Bone Dysplasia FGFR2 Type L. Slender Bone Dysplasia 1. Microcephalic Osteodysplastic Primordial Dwarfism 2. Osteocraniostenosis M. Neonatal Osteosclerotic Dysplasias 1. Bloomstrand Dysplasia 2. Caffey Disease (Infantile) 3. Raine Dysplasia N. Increased Bone Density Group 1. Osteopetrosis O. Abnormal Mineralization Group 1. Hypophosphatasia P. Multiple Epiphyseal Dysplasia and Pseudoachondroplasia Group 1. Multiple Epiphyseal Dysplasia (MED) - Autosomal Dominant 2. Multiple Epiphyseal Dysplasia (MED) - Autosomal Recessive 3. Stickler Syndrome Q. Hereditary Multiple Osteochondromas
VI. Genetic testing to establish or confirm the diagnosis of all other skeletal dysplasias or rare bone disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for coverage criteria).	VI. Genetic testing to establish or confirm the diagnosis of all other skeletal dysplasias or rare bone disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for coverage criteria).
*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.	*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly sources.