



GENETIC TESTING: SKELETAL DYSPLASIA AND RARE BONE DISORDERS (REQUIRES PREAUTHORIZATION)

V.76

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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 time they are considered bone fragility disorders.

Genetic testing has allowed for gene identification in more than two thirds of the skeletal dysplasia. 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



*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.

Dates

Original Effective
09-10-2021
Last Review
08-07-2024
Next Review
08-10-2025

REFERENCE 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.

<u>Coverage Criteria Sections</u>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes
Osteogenesis Imperfecta	Osteogenesis imperfecta COL1A1 & COL1A2 NGS Panel (CTGT Genetic Testing)	81406, 81408, 81479	Q78.0, Z82.79
	Osteogenesis Imperfecta Panel (PreventionGenetics)		
	Osteogenesis Imperfecta NGS Panel - Dominant & Recessive NGS (CTGT Genetic Testing)		
Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder	Skeletal Disorders Panel (Invitae)	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479	M85, Q77, Q78
	Skeletal Dysplasia Core & Extended NGS Panel (CTGT Genetic Testing)		
	Comprehensive Skeletal Dysplasias and Disorders Panel (Blueprint Genetics)		



Other Covered	varies	81400-81405, 81479	W100, Q11, Q10
Skeletal Dysplasias and Rare Bone Disorders			

RELATED POLICIES

V.73 Genetic Testing: Aortopathies and Connective Tissue

Disorders for coverage criteria related to Ehlers-Danlos syndrome and other connective tissue disorders.

V.62 Genetic Testing: Multisystem Inherited Disorders,

Intellectual Disability, and Developmental Delay for coverage criteria related to diagnostic testing for disorders that affect multiple systems.

V.74 Genetic Testing: General Approach to Genetic Testing 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..

POLICY

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) is 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**



inheritance, **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) for osteogenesis imperfecta is considered **investigational** for all other indications.

MULTIGENE PANEL ANALYSIS FOR SKELETAL DYSPLASIA OR RARE BONE DISORDER

I. 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:

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

II. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis



OTHER COVERED SKELETAL DYSPLASIAS 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.

I. Genetic testing to establish or confirm one of the following skeletal dysplasias or rare bone disorders to guide management is considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II 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. [Otospondylomegalopiphyseal 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



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](#)

II. 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.

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, but approximately a third of NATs are fractures.

BACKGROUND

Osteogenesis Imperfecta



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



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 >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 >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 <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 practice guideline 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



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)

Quick Code Search

Use this feature to find out if a procedure and diagnosis code pair will be approved, denied or held for review. Simply put in the procedure code, then the diagnosis code, then click "Add Code Pair". If the codes are listed in this policy, we will help you by showing a dropdown to help you.



Enter at least the first 3 characters of the code

Diagnosis

Please type a diagnosis code

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Add

CODES

+ CPT4

REFERENCES



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REVISIONS

01-01-2025

Updated Background and References

12-04-2023

Updated policy for 01/01/2024

09-29-2023

Removed "medically necessary" and replaced with "investigational" and added
"investigational when the above criteria is not met and for all other
indicatons"

06-05-2023

Reformatted and updateed references

01-01-2023

Minor table revisions and added code 81236 effective 1/1/2023

07-01-2022

Updated policy criteria, clinical considerations and references

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