

# CONCERT GENETICS GENETIC TESTING: SKELETAL DYSPLASIA AND RARE BONE DISORDERS

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See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

## OVERVIEW

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<sup>3</sup>.

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 Date of Last Revision: 04/24  
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\*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.

## POLICY REFERENCE TABLE

### Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

<a href="#">Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
<a href="#">Osteogenesis Imperfecta</a>	Osteogenesis imperfecta COL1A1 & COL1A2 NGS Panel (Connective Tissue Gene Tests)	81406, 81408, 81479	Q78.0, Z82.79	3
	Osteogenesis Imperfecta Panel (PreventionGenetics, part of Exact Sciences)			
	Osteogenesis Imperfecta NGS Panel - Dominant & Recessive Next Generation Sequencing (Connective Tissue Gene Tests)			

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<a href="#">Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder</a>	Skeletal Disorders Panel (Invitae)	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479	M85, Q77, Q78	1, 7, 8
	Skeletal Dysplasia Core & Extended NGS Panel (Connective Tissue Gene Tests)	81404, 81405, 81406, 81407, 81408, 81479		
	Comprehensive Skeletal Dysplasias and Disorders Panel (Blueprint Genetics)	81236, 81404, 81406, 81408, 81479		
<a href="#">Other Covered Skeletal Dysplasias and Rare Bone Disorders</a>				
<a href="#">Other Covered Skeletal Dysplasias and Rare Bone Disorders</a>	varies	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479	M85, Q77, Q78	2, 4, 5, 6

## OTHER RELATED POLICIES

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

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

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## CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

### 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/enrollee 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, typically with autosomal dominant 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.

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## 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/enrollee 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 3<sup>rd</sup> percentile
- II. 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.

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## 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.

- 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/enrollee 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. [Otospondylomegapiphyseal 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

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- 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](#)
- 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 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.

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## DEFINITIONS

1. **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.

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## BACKGROUND AND RATIONALE

### 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.



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- "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.

#### Laboratory features

- Serum concentrations of vitamin D, calcium, phosphorous, and alkaline phosphatase are typically normal; however, alkaline phosphatase may be elevated acutely in response to fracture and rare instances of abnormally low alkaline phosphatase levels have been noted anecdotally in severe OI.
- Analysis of type 1 collagen synthesized in vitro by culturing dermal fibroblasts obtained from a small skin biopsy reflects the structure and quantity of the collagen. The sensitivity of biochemical testing is approximately 90% in individuals with clinically confirmed OI. Biochemical analysis is essentially no longer used clinically with the advances in molecular diagnostics.

“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.

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- 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 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 gender, which is demonstrated on the standard growth curves as a length or height less than the 3rd centile. (p. 466)

*Nikkel 2017*

Nikkel (2017) indicated the value of multigene panels for skeletal dysplasias with the following:

- The use of multigene panels, using next generation sequence technology, has improved our ability to quickly identify the genetic etiology, which can impact management. (p. 419)
- One should ensure that a panel contains all the genes under consideration and there is appropriate deletion/duplication analysis when such pathogenic changes are noted to occur in the gene. (p. 420-421)
- A patient may present with a non-specific dysplasia or be too young for some of the cardinal features to be present on radiographs. There may also be significant prognostic implications regarding survival dependent upon the diagnosis, thus an urgency to get this

information. In these instances, a skeletal dysplasia gene panel can greatly reduce the time to diagnosis and can be more cost- and time-efficient rather than testing gene by gene. (p. 420)

## Other Covered Skeletal Dysplasia and Rare Bone Disorders

### *International Skeletal Dysplasia Society*

The International Skeletal Dysplasia Society published an updated categorization of skeletal dysplasias (Mortier, 2019).

This newest and tenth version of the Nosology comprises 461 different diseases that are classified into 42 groups based on their clinical, radiographic, and/or molecular phenotypes. Remarkably, pathogenic variants affecting 437 different genes have been found in 425/461 (92%) of these disorders. By providing a reference list of recognized entities and their causal genes, the Nosology should help clinicians achieve accurate diagnoses for their patients and help scientists advance research in skeletal biology. (p. 2393)

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced “coverage criteria” with “criteria. For Policy Reference Table: added “81401, 81402, 81403, 81404, 81405, 81406, 81407”. For Other Related Policies: added “and Molecular”. For Criteria; under Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder Panel: added “post-natal”; for Other Covered Skeletal Dysplasia and Rare Bone Disorders Panel: under I.O.I. removed “(also in Metabolic Policy)”; under II. added “and Molecular”.	10/23	10/23
Semi-annual review. Updated title to reflect V2.2024 version. In Overview and Clinical Considerations, policy overview updated to include information from the Clinical Considerations section, which has been consolidated into the Overview section. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	04/24	04/24

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### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health

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plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid member/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take

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precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare member/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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