Medica Coverage Policy

Policy Name:	**Genetic Testing: Skeletal Dysplasia and Rare Bone Disorders**
Medica Effective Date:	**January 01, 2024**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between policy requirements and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

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.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Osteogenesis	Osteogenesis imperfecta COL1A1 & COL1A2	81406, 81408,	Q78.0, Z82.79	3

Imperfecta	NGS Panel (CTGT Genetic Testing)	81479		
	Osteogenesis Imperfecta Panel (PreventionGenetics, part of Exact Sciences)			
	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	1, 7, 8
	Skeletal Dysplasia Core & Extended NGS Panel (CTGT Genetic Testing)			
	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	M85, Q77, Q78	2, 4, 5, 6

OTHER 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.

COVERAGE 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 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.

back to top

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 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**, AND**

B. The differential diagnosis includes more than one type of skeletal dysplasia or bone disorder.

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.

back to top

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 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. 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

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 source.

back to top

PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

NOTES AND DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives:

   a. **First-degree relatives** are parents, siblings, and children

   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

2. **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.

back to top

CLINICAL CONSIDERATIONS

Osteogenesis Imperfecta versus Non-accidental trauma (NAT)
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. 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 discussion of non-accidental trauma is as follows:
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.

back to top

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.
- "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.
- 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)

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)

back to top

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. Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A. 2019;179(12):2393-2419. doi:10.1002/ajmg.a.61366
3. Steiner RD, Basel D. COL1A1/2 Osteogenesis Imperfecta. 2005 Jan 28 [Updated 2021 May 6]. In: Adam MP, Mirzaa GM Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1295/
4. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
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. Nikkel SM. Skeletal Dysplasias: What Every Bone Health Clinician Needs to Know. Curr Osteoporos Rep. 2017;15(5):419-424. doi:10.1007/s11914-017-0392-x
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

back to top

Medica Original Effective Date: February 20, 2023
- Concert Genetics Effective Date: January 01, 2023 (V.1.2023)

Medica Re-Review Date(s):
- June 21, 2023
  - Concert Genetics Effective Date: July 01, 2023 (V.2.2023)
- December 20, 2023
  - Concert Genetics Effective Date: January 01, 2024 (V.12024)