Clinical Policy: Genetic Testing Skeletal Dysplasia and Rare Bone Disorders

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Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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[3]. 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.

Below is a list of higher volume tests and the associated laboratories for each criteria section. This list is not all inclusive.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81408, 81479	COL1A1 Sequencing Analysis COL1A2 Sequencing Analysis	Osteogenesis Imperfecta	Q78.0, Z82.79
81408, 81479	Osteogenesis Imperfecta Panel (PreventionGenetics)	Osteogenesis Imperfecta	Q78.0, Z82.79
81408, 81479	Osteogenesis Imperfecta NGS Panel - Dominant & Recessive NGS (CTGT)	Osteogenesis Imperfecta	Q78.0, Z82.79
81408, 81479	Osteogenesis Imperfecta and Decreased Bone Density NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)	Osteogenesis Imperfecta	Q78.0, Z82.79
81400, 81401, 81402, 81403, 81404, 81405,	Invitae Skeletal Disorders Panel (Invitae)	Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder	M85, Q77, Q78

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81406, 81407, 81408, 81479	Skeletal Dysplasia Core NGS Panel (CTGT) Skeletal Dysplasia Core NGS Panel (CTGT) Skeletal Dysplasia Core & Extended NGS Panel (CTGT) Comprehensive Skeletal Dysplasias and Disorders Panel (Blueprint Genetics)		
81400-81408, 81479	Varies	Other Skeletal Dysplasias and Rare Bone Disorders	N/A

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

- ***CP.MP.215 Genetic Testing: Aortopathies and Connective Tissue Disorders*** for criteria related to Ehlers-Danlos syndrome and other connective tissue disorders.
- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic testing for disorders that affect multiple systems.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to skeletal dysplasias and rare bone disorders that is not specifically discussed in this or another non-general policy.

Policy/Criteria

Osteogenesis Imperfecta

I. It is the policy of health plans affiliated with Centene Corporation® that *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81408, 81479) to establish or confirm a diagnosis of osteogenesis imperfecta (OI) is considered **medically necessary** when meeting any of the following:

   A. The member/enrollee has fractures with minimal or no trauma in the absence of other factors, such as non-accidental trauma (NAT) (see definitions) or other known disorders of bone,

   B. The member/enrollee has two or more of the following clinical features of osteogenesis imperfecta:

      1. Characteristic triangular facies
      2. Blue sclerae persistent after infancy
      3. Ligamentous laxity
      4. Dentinogenesis imperfecta
      5. Progressive, postpubertal hearing loss

6. Fractures of varying ages and stages of healing (often of the long bones)
7. "Codfish" vertebrae
8. Wormian bones
9. Protrusio acetabuli
10. Low bone mass,

C. The member/enrollee has a close relative[1] diagnosed with osteogenesis imperfecta and one or more of the following:

1. Characteristic triangular facies
2. Blue sclerae persistent after infancy
3. Ligamentous laxity
4. Dentinogenesis imperfecta
5. Progressive, postpubertal hearing loss
6. Fractures of varying ages and stages of healing (often of the long bones)
7. "Codfish" vertebrae
8. Wormian bones
9. Protrusio acetabuli
10. Low bone mass

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81408, 81479) to establish or confirm a diagnosis of osteogenesis imperfecta for all other indications.

Multigene Panel Analysis for Skeletal Dysplasia or Rare Bone Disorder

I. It is the policy of health plans affiliated with Centene Corporation® that multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder may be considered **medically necessary** when meeting both of the following:

A. The member/enrollee displays one or more of the following clinical features of a skeletal dysplasia:

1. Shortening of the bones of the arms and legs >3 standard deviations below the mean,

2. Head circumference > 90th percentile,

3. Bone irregularities (e.g., bowed, fractured, thickened, thin, undermineralized, etc.),

4. Abnormal ribs or a small chest circumference,

5. Short stature with height/length < 3rd percentile and both of the following:
   a) Negative evaluation for an endocrine disorder (e.g. constitutional growth delay, primary endocrinopathy)
   b) Non-genetic causes of short stature,

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder is considered **investigational** for all other indications.

Other Skeletal Dysplasia and Rare Bone Disorders

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

I. It is the policy of health plans affiliated with Centene Corporation® that 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. 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 (also in Metabolic Policy)

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. It is the policy of health plans affiliated with Centene Corporation® that 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 *CP.MP.222 General Approach to Genetic 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.

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.

Non-accidental trauma (NAT)

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.

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 2021, 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.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
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References

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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 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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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