Hereditary Connective Tissue and Thoracic Aortic Disease Genetic Testing

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Introduction

Hereditary connective tissue and thoracic aortic disease genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Aortic dysfunction or dilation duplication/ deletion analysis panel	81411
Aortic dysfunction or dilation genomic sequencing analysis panel	81410
Hereditary connective tissue and thoracic aortic disease gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479

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Procedures addressed by this guideline	Procedure codes
Hereditary connective tissue and thoracic aortic disease known familial mutation analysis	81403

Criteria

Introduction

Requests for hereditary connective tissue disorder (HCTD) genetic testing, including testing for thoracic aortic aneurysms and dissections (TAAD), are reviewed using the following criteria.

HCTD Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic or Predisposition Testing for an Autosomal Dominant HCTD:
  - Known familial mutation in a 1st or 2nd degree biological relative, OR
- Diagnostic or Predisposition Testing for an Autosomal Recessive HCTD:
  - Known familial mutation in a 1st, 2nd, or 3rd degree biological relative, OR
- Diagnostic or Predisposition Testing for an X-linked HCTD:
  - Known familial mutation in a 1st, 2nd, or 3rd degree biological relative and the individual is at risk for inheriting the familial mutation based on an X-linked inheritance pattern, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HCTD Single-Gene Testing

Sequencing and/or duplication/deletion analysis of a single gene is considered medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing that would have included the requested gene, and

    - The member does not have a family history of a known gene mutation that would explain their clinical symptoms, AND
- Diagnostic Testing in Symptomatic Individuals:
    - The member has multiple clinical features consistent with the condition for which testing is requested (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for specific examples), and
    - The member does not have a known underlying cause for their symptoms (e.g. pathogenic or likely pathogenic mutation, clinical diagnosis of hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder), and
    - A genetic diagnosis would result in changes to the member's medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HCTD Multigene Sequencing Panels

Multigene sequencing panels, including syndrome-specific panels (e.g., Ehlers-Danlos syndrome panels, Stickler syndrome panels) or multi-syndrome panels (e.g., combined Marfan/Loeys-Dietz/TAAD panels, Connective Tissue Disorder panels), are considered medically necessary when the following criteria are met:

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
    - No previous multigene sequencing for the suspected condition(s), and
    - The member does not have a family history of a known gene mutation that would explain their clinical symptoms, AND
- Diagnostic Testing in Symptomatic Individuals:
    - The member has, or is suspected of having, a condition that will benefit from information provided by the requested panel based on one of the following:
        - Documentation from the ordering provider indicating clinical suspicion for Ehlers-Danlos syndrome (EDS), and
            - The member meets 2017 International Criteria for at least one type of EDS included on the panel (excluding hypermobile type), and/or
        - Documentation from the ordering provider indicating clinical suspicion for at least one non-EDS HCTD included on the panel, and
            - The member has multiple clinical features consistent with the suspected condition(s) (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for specific examples), and/or
        - Member's cardiovascular examination consistent with TAAD (e.g., aortic root or ascending aortic diameter ≥4.0 cm, Z score ≥2, or dissection), and
            - Absence of known ectopia lentis, and

        - The panel includes, at minimum, the FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK genes, and
    - The member does not have a known underlying cause for their symptoms (e.g. pathogenic/likely pathogenic mutation, clinical diagnosis of hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder), and
    - A genetic diagnosis would result in changes to the member's medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HCTD Multigene Deletion/Duplication Analysis Panels

- Member meets criteria for HCTD Multigene Sequencing Panels, AND
- Previous HCTD multigene sequencing panel performed with one of the following results:
    - No pathogenic or likely pathogenic mutation identified, or
    - One pathogenic or likely pathogenic mutation identified in a gene associated with an autosomal recessive condition, AND
- No previous multigene deletion/duplication panel for the suspected condition, AND
- Rendering laboratory is a qualified provider for service per Health Plan policy.

Exclusions and Other Considerations

- This guideline may not apply to genetic testing for indications that are specifically addressed elsewhere. HCTDs that commonly present with joint, cutaneous, cardiovascular, and/or ocular features are the focus of this guideline.
- Germline genetic testing is only medically necessary once per lifetime. Therefore, a single gene included in a panel may not be medically necessary if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest (e.g., testing a single new gene, or a panel with multiple new genes, that have a definitive association with TAAD according to the **ClinGen Gene-Disease Validity Curation**).
- Genetic testing is not medically necessary for the following indications:
    - Personal and/or family history consistent with hypermobile EDS (formerly EDS type III), hypermobility spectrum disorders (formerly "joint hypermobility syndromes"), or isolated joint hypermobility
    - Definitive clinical diagnosis of Marfan syndrome due to having both aortic root dilation and ectopia lentis, without features suggesting an alternative disorder.
        - Exceptions for single-gene (FBN1) testing may be considered on a case-by-case basis (e.g., when required for clinically appropriate treatment or surveillance of the member).

- If genetic testing is requested for the purpose of facilitating diagnosis of at-risk family members, including at-risk pregnancies, please refer to the guideline, *Genetic Testing to Diagnose Non-Cancer Conditions*, as this indication is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - Both the sequencing and deletion/duplication components of genetic testing for clinically indicated gene(s) will be reimbursed.
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81410 or 81479*).
    - When deletion/duplication testing is not part of a single panel CPT code being billed, it is separately reimbursable when billed with a single CPT code specific to the performed deletion/duplication analysis panel (e.g., 81411*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

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What are hereditary connective tissue and thoracic aortic diseases?

Hereditary connective tissue disorders (HCTDs) are a group of disorders that affect the connective tissues that support the skin, bones, joints, heart, blood vessels, eyes, and other organs.[1] There are more than 200 connective tissue disorders.[2]

HCTDs that primarily affect bone development (e.g., skeletal dysplasia, osteogenesis imperfecta, and other rare bone disorders) are not addressed by this guideline.

Prevalence

Although connective tissue disorders as a whole are common, individual hereditary connective tissue disorders are relatively uncommon:

- Familial thoracic aortic aneurysms and dissections (TAAD) is estimated to account for approximately 20% of all cases of TAAD.[3]
- Ehlers-Danlos syndrome (EDS) is estimated to occur in approximately 1 in 5,000 individuals.[1,4] Hypermobile EDS and the related "hypermobility spectrum disorders" are by far the most common types, and their combined prevalence may be as high as 1 in 500.[5] Other EDS types are much rarer.[1,4]
- Marfan syndrome is estimated to occur in 1 to 5 per 10,000 individuals.[1,6]
- The exact prevalence is unknown for Loeys-Dietz syndrome, Stickler syndrome, and other rare HCTDs.[7-13]

Symptoms

While specific features vary by type, the following are present in many HCTDs:

• **Joint hypermobility**	Joint hypermobility is an unusually large range of joint movement, which may be asymptomatic or associated with musculoskeletal complications such as chronic pain and disturbed proprioception.[14,15]
• **Thoracic aortic aneurysms and aortic dissections (TAAD)**	TAAD typically involves aneurysms (bulges) in the aortic root and ascending aorta.[16] Most aneurysms are asymptomatic; however, if undetected and untreated, they can lead to aortic dissection (a tear within the aortic wall), which is a life-threatening condition.[16] TAAD may occur as part of a syndromic HCTD (e.g., Marfan syndrome or Loeys-Dietz syndrome) involving multiple organ systems or as an isolated finding (referred to as "nonsyndromic TAAD").[16,17]

A detailed description of all HCTDs is beyond the scope of this guideline. Please see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for a summary of some of the most common types.

Cause and Inheritance

Associated genes have been identified for many HCTDs, and medical management may differ based on the underlying genetic etiology.[1] Inheritance patterns vary by type and include autosomal dominant, autosomal recessive, and X-linked inheritance.

Some of the most common types of HCTDs and associated genes are summarized below:

Table: Select Hereditary Connective Tissue and Thoracic Aortic Diseases

This table is not intended to be all-inclusive; other genes/disorders not listed here may have coverage under this guideline. Many genes in this table are also associated with other disorders that are not described here (e.g., osteogenesis imperfecta, skeletal dysplasia, etc.). Genetic testing should be reviewed for the appropriate condition/indication.

Disorder	Clinical Features	Genes & Inheritance
ACTA2-related disorders (including smooth muscle dysfunction syndrome)[16,18]	TAAD; patent ductus arteriosus; moyamoya-like cerebrovascular disease; early-onset coronary artery disease; iris flocculi; livedo reticularis; pulmonary disease; congenital mydriasis (fixed, dilated pupils); hypoperistalsis of the gut; and/or hypotonic bladder	ACTA2 (AD)
Arterial tortuosity syndrome[9]	Severe and widespread elongation and tortuosity of the aorta and mid-sized arteries along with any of the following: characteristic facial features; evidence of a generalized connective tissue disorder (e.g., joint hypermobility, skin involvement, and/or hernias); skeletal findings (e.g., pectus deformities, arachnodactyly, scoliosis, contractures, and/or camptodactyly)	SLC2A10 (AR)

Disorder	Clinical Features	Genes & Inheritance
Congenital contractural arachnodactyly (CCA or Beals syndrome)[10]	Arachnodactyly with positive wrist and thumb sign; flexion contractures of multiple joints (elbows, knees, hips, ankles, and/or fingers); kyphoscoliosis; abnormal ears ("crumpled" outer helices); and/or a marfanoid habitus. A clinical diagnostic scoring system is also available.	FBN2 (AD)
Cutis laxa[11,19]	Lax, sagging skin causing a droopy appearance to the face and other parts of the body; wrinkled skin that is particularly noticeable on the neck and in the armpits and groin; TAAD; emphysema; and/or inguinal or umbilical hernia	ELN, FBLN5, ALDH18A1 (AD) ATP6V0A2, EFEMP2, LTBP4, PYCR1 (AR) ATP7A (XL)
Ehlers-Danlos Syndrome (EDS)[4,5,20]	Generalized joint hypermobility, subluxations/ dislocations; characteristic skin findings (e.g., hyperextensibility, fragility, poor healing, atrophic scars); organ or vascular rupture; severe cardiac valvular disease; and/or marked muscular, skeletal or ocular findings seen in rare EDS types (see "Diagnosis" section for 2017 International Criteria).*	COL5A1, COL5A2, COL3A1, COL1A1 (AD) TNXB, AEBP1, ADAMTS2 (AR) COL1A2 (AD or AR)
FLNA deficiency[12]	A family history consistent with X-linked inheritance (which may include male lethality), and any combination of the following: neuroimaging features (especially periventricular nodular heterotopia [PVNH]); seizures; cardiovascular findings (e.g., TAAD, valvular heart disease, structural heart disease); pulmonary findings; gastrointestinal manifestations; and/or joint hypermobility	FLNA (XL)

Disorder	Clinical Features	Genes & Inheritance
Loeys-Dietz syndrome (LDS)[7]	Vascular findings (TAAD, other arterial aneurysms or tortuosity); skeletal findings (e.g., pectus deformities, scoliosis, joint laxity or contracture, arachnodactyly, talipes equinovarus, cervical spine malformation or instability, early-onset osteoarthritis); characteristic craniofacial features (hypertelorism, bifid uvula / cleft palate, craniosynostosis); cutaneous involvement (e.g., translucent skin with easily visible underlying veins, atrophic scarring, easy bruising); dural ectasia (stretching of the dural sac); allergic / inflammatory disease; and/or blue sclerae	TGFBR2, TGFBR1, SMAD3, TGFB2, TGFB3, SMAD2 (AD) IPO8 (AR)
Marfan syndrome (MFS)[6]	TAAD; ectopia lentis (dislocated lens of the eye); and/or a combination of features including specific skeletal, ocular, cardiovascular, cutaneous and/or craniofacial findings (see "Diagnosis" section for Ghent clinical diagnostic criteria)	FBN1 (AD)
Nonsyndromic thoracic aortic aneurysm and dissection (nsTAAD; also called familial TAAD)[3,16,17]	TAAD, with or without other cardiovascular findings (e.g., patent ductus arteriosus, bicuspid aortic valve), in the absence of systemic features. The genes to the right have been classified as having a definitive association with nsTAAD.**	ACTA2, COL3A1, FBN1, MYH11, MYLK, SMAD3, TGFB2, TGFBR1, TGFBR2 (AD)
NOTCH1-related cardiovascular disorders[16,18]	Bicuspid aortic valve with an associated risk for TAAD and/or other congenital cardiac malformations involving the left ventricular outflow tract (LVOT)	NOTCH1 (AD)
Shprintzen-Goldberg syndrome (SGS)[13]	Developmental delay or intellectual disability; characteristic craniofacial features; craniosynostosis involving the coronal, sagittal, or lambdoid sutures; and/or musculoskeletal findings (C1-C2 spine malformation, joint contractures, clubfeet)	SKI (AD)

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Disorder	Clinical Features	Genes & Inheritance
Stickler syndrome[8,21]	Ocular findings (myopia, cataract, retinal detachment, and/or vitreous abnormalities); hearing loss; craniofacial findings*** (midfacial underdevelopment and/or cleft palate, which may occur as part of Pierre Robin sequence); mild spondyloepiphyseal dysplasia; and/or early-onset arthritis	COL2A1, COL11A1, COL11A2 (AD) COL9A1, COL9A2, COL9A3 (AR)

Note:

AD: autosomal dominant inheritance; **AR:** autosomal recessive inheritance; **XL:** X-linked inheritance; *Gene list for EDS is not all-inclusive. Additional genes associated with rare types are listed in the "Diagnosis" section of this guideline. The genetic etiology of hypermobile EDS is unknown.[20] **Gene list for nsTAAD is not all-inclusive. Genes with a strong or moderate association include LOX, PRKG1, EFEMP2, FOXE3, MFAP5, and SMAD2, while other, unlisted genes have a limited association.[16,17] ***Pierre Robin sequence is a group of related malformations that includes micrognathia (small mouth), glossoptosis (tongue displaced towards the back of the oral cavity), and cleft palate; cleft lip is NOT a feature of Stickler syndrome.[21]

Diagnosis

HCTDs may be diagnosed through a combination of clinical evaluation, cardiac imaging, and/or molecular testing (when the causative genes for the suspected disorder are known).[1] Clinical diagnostic criteria are available for a few HCTDs, including Marfan syndrome and Ehlers-Danlos syndrome.[6,10,19,22,23] Since it can sometimes be difficult to reliably identify a specific condition based on clinical and family history alone, many diagnostic criteria have also incorporated genetic testing.

Clinical evaluation by a specialist familiar with HCTDs may help narrow the differential to one condition or group of conditions.[1] An ophthalmology examination may be performed to identify eye findings associated with HCTDs, such as ectopia lentis characteristic of Marfan syndrome.[6] Physical examination may identify craniofacial, cutaneous, and musculoskeletal features. Joint hypermobility can be evaluated with calculation of a 9-point Beighton score, a 5-point questionnaire, and assessment for comorbidities.[14,15,20] The Beighton scoring system assesses the flexibility of multiple joints and is scored as follows:[15,20]

- Adults ≤ 50 years of age with a Beighton score of ≥5, adults >50 years of age with a Beighton score ≥4, and pre-pubertal children and adolescents with a Beighton score ≥6, are considered to have generalized joint hypermobility.
- In individuals with a Beighton score 1 point below the age-specific cut-off, a positive 5-point questionnaire result can be taken as evidence of generalized joint hypermobility.
- Assessment for generalized joint hypermobility is considered inaccurate in children under the age of 5 years.

Cardiac imaging is important for the evaluation of HCTDs and may utilize echocardiography, CT, or MRI to detect associated cardiovascular features, including TAAD.[16] An aortic diameter ≥4.0 cm to 4.4 cm is defined as aortic dilation, while a diameter ≥4.5 cm is defined as an aortic aneurysm.[18] However, these thresholds may be less accurate in individuals whose height and/or body surface area are not within 1 to 2 standard deviations of the mean. A Z score is used to normalize aortic root and ascending aorta diameters for body size, particularly in the pediatric population.[16,18]

Clinical genetic testing is available for many HCTDs and may be used to confirm the diagnosis when clinically suspected.[1] Hypermobile EDS and the related hypermobility spectrum disorders (formerly "joint hypermobility syndrome") continue to require a clinical diagnosis, as their genetic etiologies are not yet known.[1,5,24] While the diagnostic yield of genetic testing is high in individuals with features of a syndromic TAAD, individuals with familial, nonsyndromic TAAD will only have an identifiable mutation in ~20-30% of cases.[16]

Diagnostic Criteria for Heritable Thoracic Aortic Disease

A diagnosis of heritable thoracic aortic disease (HTAD, which includes TAAD) can be established in an individual with any of the following:[16]

- Highly penetrant pathogenic mutation(s) in a known HTAD gene, and/or
- Thoracic aortic disease and one or more additional family member(s) with thoracic aortic disease, and/or
- Thoracic aortic disease with specific clinical features of a syndrome associated with thoracic aortic disease (e.g., Marfan syndrome, Loeys-Dietz syndrome)

Ghent Criteria for Marfan Syndrome

A clinical diagnosis of Marfan syndrome is made according to Ghent Criteria.[6,22,23]

With no known family history, a Marfan syndrome diagnosis is confirmed if any ONE of the following is met:[6,22,23]

- Significant aortic dilation (Z-score ≥2)/dissection + ectopia lentis**
- Significant aortic dilation (Z-score ≥2)/dissection + FBN1 mutation
- Aortic dilation/dissection + sufficient points from other system findings**
- Ectopia lentis + FBN1 mutation known to be associated with aortic disease

With a known family history, the presence of any ONE of the following is diagnostic:[6,22,23]

- Ectopia lentis
- Significant aortic root enlargement (Z-score ≥2 in those >20 years of age or ≥3 in those <20 years of age)**
- Sufficient points (≥7) from other system findings**

** Marfan syndrome can be clinically diagnosed in these cases, provided there are not other findings that more strongly suggest conditions with clinical overlap, such as Sphrintzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome, or these conditions are unlikely based on genetic or collagen testing.

Systemic scoring system[6,22,23]

- Wrist and thumb sign - 3 points
- Wrist or thumb sign - 1 point
- Pectus carinatum deformity - 2 points
- Pectus excavatum or chest asymmetry -1 point
- Hindfoot deformity - 2 points
- Plan pes planus -1 point
- Pneumothorax - 2 points
- Dural ectasia - 2 points
- Protrusio acetabulae - 2 points
- Reduced upper seg/lower seg and inc. arm span/height ratios - 1 point
- Scoliosis or thoracolumbar kyphosis - 1 point
- Reduced elbow extension - 1 point
- 3 of 5 facial features: Dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia - 1 point
- Skin striae - 1 point
- Myopia - 1 point
- Mitral valve prolapse - 1 point

According to the Ghent criteria, many of the manifestations of Marfan syndrome can emerge with age. Therefore, it is not advisable to establish definitive alternative diagnosis in individuals younger than age 20 years who have some physical manifestations of Marfan syndrome but not enough for a clinical diagnosis. In this circumstance, the following is suggested:[22]

- "If the systemic score is <7 and/or borderline aortic root measurements (Z-score <3) are present (without an FBN1 pathogenic variant), use of the term "nonspecific connective tissue disorder" is suggested until follow-up echocardiographic evaluation shows aortic root dilation (Z-score ≥3)."

- "If an FBN1 pathogenic variant is identified in simplex or familial cases but aortic root Z-score is below 3.0, the term 'potential Marfan syndrome' should be used until the aorta reaches this threshold."

2017 International Criteria for EDS

As defined in the sections below, an International Consortium developed clinical criteria for EDS.[20]

Classical EDS

Molecular basis: Heterozygous mutations in either COL5A1 or COL5A2 for >90% of cases; rarely, specific heterozygous COL1A1 mutations or biallelic COL1A2 mutations

Minimal criteria suggestive for Classical EDS (cEDS) are met when the following are present:

- Skin hyperextensibility and atrophic scarring, PLUS either of the following:
  - Generalized joint hypermobility
  - Three or more of the following features:
    - Easy bruising
    - Soft, doughy skin
    - Skin fragility (or traumatic splitting)
    - Molluscoid pseudotumors
    - Subcutaneous spheroids
    - Hernia (or history thereof)
    - Epicanthal folds
    - Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
    - Family history of a first-degree relative who meets clinical criteria

Classical-like EDS

Molecular basis: Biallelic TNXB mutations/deletions or AEBP1 mutations*

Minimal criteria suggestive for Classical-like EDS (clEDS) are met when ALL of the following are present:

- Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring
- Generalized joint hypermobility with or without recurrent dislocations (most commonly shoulder and ankle)
- Easy bruisable skin/spontaneous ecchymoses
- A family history compatible with autosomal recessive transmission

Minor criteria for clEDS include:

- Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules
- Edema in the legs in absence of cardiac failure
- Mild proximal and distal muscle weakness
- Axonal polyneuropathy
- Atrophy of muscles in hands and feet
- Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly
- Vaginal/uterus/rectal prolapse

Note:

*TNXB was the only gene known to be associated with clEDS when the 2017 International Criteria were published.[20] AEBP1 was later identified as an EDS gene associated with a clinical presentation resembling clEDS.[25] This gene and its associated phenotype have not yet been classified by the International Consortium.

Cardiac-Valvular EDS

Molecular basis: Specific types of biallelic COL1A2 mutations

Minimal criteria suggestive for Cardiac-Valvular EDS (cvEDS) are met when BOTH of the following are present:

- Severe progressive cardiac-valvular problems (aortic valve, mitral valve)
- A family history compatible with autosomal recessive inheritance, PLUS either of the following:
  - One or more of the following features:
    - Skin involvement: skin hyperextensibility, atrophic scars, thin skin, easy bruising
    - Joint hypermobility (generalized or restricted to small joints)
  - Two or more of the following features:
    - Inguinal hernia
    - Pectus deformity (especially pectus excavatum)
    - Joint dislocations
    - Foot deformities: pes planus, pes planovalgus, hallux valgus

Vascular EDS

Molecular basis: Heterozygous mutations in COL3A1 or (rarely) specific heterozygous mutations in COL1A1

Minimal criteria suggestive for Vascular EDS (vEDS) are met when AT LEAST ONE of the following is present:

- A family history of the disorder

- Arterial rupture or dissection in individuals less than 40 years of age
- Unexplained sigmoid colon rupture (i.e. in the absence of known diverticular disease or other bowel pathology)
- Spontaneous pneumothorax in the presence of other features consistent with vEDS
- Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
- Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma
- A combination of the following features:
  - Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
  - Thin, translucent skin with increased venous visibility
  - Characteristic facial appearance
  - Spontaneous pneumothorax
  - Acrogeria
  - Talipes equinovarus
  - Congenital hip dislocation
  - Hypermobility of small joints
  - Tendon and muscle rupture
  - Keratoconus
  - Gingival recession and gingival fragility
  - Early onset varicose veins (under 30 and nulliparous if female)

Hypermobile EDS

Molecular basis: Unknown; clinical diagnosis required

Diagnosis of Hypermobile EDS (hEDS) requires all of the following criteria (1 AND 2 AND 3) to be met:

- Criteria 1: Generalized joint hypermobility
- Criterion 2: Two or more among the features (A-C) listed in the table below must be present (for example: A and B; A and C; B and C; A and B and C)
- Criterion 3: All of the following prerequisites are met:
  - Absence of unusual skin fragility
  - Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions
  - Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity.

Feature A (a total of 5 must be present):

- Unusually soft or velvety skin
- Mild skin hyperextensibility

- Unexplained striae
- Bilateral piezogenic papules of the heel
- Recurrent or multiple abdominal hernia(s)
- Atrophic scarring involving at least two sites
- Pelvic floor, rectal, and/or uterine prolapes in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- Dental crowding and high or narrow palate
- Arachnodactyly
- Arm span-to-height ≥ 1.05
- Mitral valve prolapse (MVP)
- Aortic root dilatation with Z-score > +2

Feature B: Positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS

Feature C (must have at least one):
- Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months.
- Chronic, widespread pain for ≥ 3 months
- Recurrent joint dislocations or frank joint instability, in the absence of trauma, based on at least one of the following:
  - Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
  - Medical confirmation of joint instability at two or more sites not related to trauma

Arthrochalasia EDS

Molecular basis: Specific types of heterozygous mutations in either COL1A1 or COL1A2

Minimal criteria suggestive for Arthrochalasia EDS (aEDS) are met when the following are present:
- Congenital bilateral hip dislocation, PLUS either of the following:
  - Skin hyperextensibility
  - Severe generalized joint hypermobility, with multiple dislocations/ subluxations, and two or more of the following features:
    - Muscle hypotonia
    - Kyphoscoliosis
    - Radiologically mild osteopenia
    - Tissue fragility, including atrophic scars
    - Easy bruisable skin

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Dermatosparaxis EDS

Molecular basis: Biallelic mutations in ADAMTS2

Minimal criteria suggestive for Dermatosparaxis EDS (dEDS) are met when BOTH of the following are present:

- Extreme skin fragility with congenital or postnatal skin tears
- Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood, PLUS either of the following:
  - One or more of the following features:
    - Redundant, almost lax skin, with excessive skin folds at the wrist and ankles
    - Increased palmar wrinkling
    - Severe bruisability with a risk of subcutaneous hematomas and hemorrhage
    - Umbilical hernia
    - Postnatal growth retardation
    - Short limbs, hands and feet
    - Perinatal complications due to connective tissue fragility
  - Three or more of the following features:
    - Soft and doughy skin texture
    - Skin hyperextensibility
    - Atrophic scars
    - Generalized joint hypermobility
    - Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse)
    - Delayed motor development
    - Osteopenia
    - Hirsutism
    - Tooth abnormalities
    - Refractive errors (myopia, astigmatism)
    - Strabismus

Kyphoscoliotic EDS

Molecular basis: Biallelic mutations in either PLOD1 or FKBP14

Minimal criteria suggestive for Kyphoscoliotic EDS (kEDS) are met when BOTH of the following are present:

- Congenital muscle hypotonia
- Congenital or early onset kyphoscoliosis (progressive or non-progressive), PLUS either of the following:

- Generalized joint hypermobility with dislocations/subluxations (shoulders, hips, and knees in particular)
- Three or more of the following features (either general or gene-specific):
  - General:
    - Skin hyperextensibility
    - Easy bruisable skin
    - Rupture/aneurysm of a medium-sized artery
    - Osteopenia/osteoporosis
    - Blue sclerae
    - Hernia (umbilical or inguinal)
    - Pectus deformity
    - Marfanoid habitus
    - Talipes equinovarus
    - Refractive errors (myopia, hypermetropia)
  - PLOD1-specific:
    - Skin fragility (easy bruising, friable skin, poor wound healing), widened atrophic scarring
    - Scleral and ocular fragility/rupture
    - Microcornea
    - Facial dysmorphology
  - FKBP14-specific:
    - Congenital hearing impairment (any type)
    - Follicular hyperkeratosis
    - Muscle atrophy
    - Bladder diverticula

Brittle Cornea Syndrome (BCS)

Molecular basis: Biallelic mutations in either ZNF469 or PRDM5

Minimal criteria suggestive for Brittle Cornea Syndrome (BCS) are met when the following are present:

- Thin cornea, with or without rupture (central corneal thickness often <400 µm), PLUS either of the following:
  - One or more of the following features:
    - Early onset progressive keratoconus
    - Early onset progressive keratoglobus
    - Blue sclerae
  - Three or more of the following features:
    - Enucleation or corneal scarring as a result of previous rupture
    - Progressive loss of corneal stromal depth, especially in central cornea

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        - High myopia, with normal or moderately increased axial length
        - Retinal detachment
        - Deafness (often mixed, progressive, higher frequencies often more severely affected)
        - Hypercompliant tympanic membranes
        - Developmental dysplasia of the hip
        - Hypotonia in infancy, usually mild if present
        - Scoliosis
        - Arachnodactyly
        - Hypermobility of distal joints
        - Pes planus, hallux valgus
        - Mild contractures of fingers (especially fifth)
        - Soft, velvety skin, translucent skin

Spondylodysplastic EDS

Molecular basis: Biallelic mutations in B4GALT7, SLC39A13, or B3GALT6

Minimal criteria suggestive for Spondylodysplastic EDS (spEDS) are met when ALL of the following are present:

- Short stature (progressive in childhood)
- Muscle hypotonia (ranging from severe congenital, to mild later-onset)
- Characteristic radiographic findings (e.g. bowing of limbs)
- Three or more of the following features (general or gene-specific):
    - General:
        - Skin hyperextensibility, soft, doughy skin, thin translucent skin
        - Pes planus
        - Delayed motor development
        - Osteopenia
        - Delayed cognitive development
    - B4GALT7-specific:
        - Radioulnar synostosis
        - Bilateral elbow contractures or limited elbow movement
        - Generalized joint hypermobility
        - Single transverse palmar curve
        - Characteristic craniofacial features
        - Characteristic radiographic findings
        - Severe hypermetropia
        - Clouded cornea
    - SLC39A13-specific:

        - Protuberant eyes with bluish sclerae
        - Hands with finely wrinkled palms
        - Atrophy of the thenar muscles, tapering fingers
        - Hypermobility of distal joints
        - Characteristic radiologic findings
    - B3GALT6-specific:
        - Kyphoscoliosis (congenital or early onset, progressive)
        - Joint hypermobility, generalized or restricted to distal joints, with joint dislocations
        - Joint contractures (congenital or progressive) (especially hands)
        - Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges)
        - Talipes equinovarus
        - Characteristic craniofacial features
        - Tooth discoloration, dysplastic teeth
        - Characteristic radiographic findings
        - Osteoporosis with multiple spontaneous fractures Ascending aortic aneurysm
        - Lung hypoplasia, restrictive lung disease

Musculocontractural EDS

Molecular basis: Biallelic mutations in CHST14 or (rarely) DSE

Minimal criteria suggestive for Musculocontractural EDS (mcEDS) are met with EITHER of the following:

- At birth or in early childhood when both of the following are present:
    - Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot)
    - Characteristic craniofacial features, which are evident at birth or in early infancy
- In adolescence and in adulthood when both of the following are present:
    - Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot)
    - Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling

Minor criteria for mcEDS include:

- Recurrent/chronic dislocations
- Pectus deformities (flat, excavated)
- Spinal deformities (scoliosis, kyphoscoliosis)
- Peculiar fingers (tapering, slender, cylindrical)

- Progressive talipes deformities (valgus, planus, cavum)
- Large subcutaneous hematomas
- Chronic constipation
- Colonic diverticula
- Pneumothorax/pneumohemothorax
- Nephrolithiasis/cystolithiasis
- Hydronephrosis
- Cryptorchidism in males
- Strabismus
- Refractive errors (myopia, astigmatism)
- Glaucoma/elevated intraocular pressure

Myopathic EDS

Molecular basis: Heterozygous or biallelic mutations in COL12A1

Minimal criteria suggestive for Myopathic EDS (mEDS) are met when the following are present:

- Congenital muscle hypotonia, and/or muscle atrophy, that improves with age, PLUS either of the following:
  - One or more of the following features:
    - Proximal joint contractures (knee, hip, and elbow)
    - Hypermobility of distal joints
  - Three or more of the following features:
    - Soft, doughy skin
    - Atrophic scarring
    - Motor developmental delay
    - Myopathy on muscle biopsy

Periodontal EDS

Molecular basis: Heterozygous gain-of-function mutations in either C1R or C1S

Minimal criteria suggestive for Periodontal EDS (pEDS) are met when BOTH of the following are present:

- Either of the following combinations of features:
  - Severe and intractable periodontitis of early onset (childhood or adolescence), and two or more of the following features:
    - Lack of attached gingiva
    - Pretibial plaques
    - Family history of a first-degree relative who meets clinical criteria
  - Lack of attached gingiva, and both of the following features:
    - Pretibial plaques

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        - Family history of a first-degree relative who meets clinical criteria
    - One or more of the following features:
        - Easy bruising
        - Joint hypermobility, mostly distal joints
        - Skin hyperextensibility and fragility, abnormal scarring (wide or atrophic)
        - Increased rate of infections
        - Hernias
        - Marfanoid facial features
        - Acrogeria
        - Prominent vasculature

Joint Hypermobility and Hypermobility Spectrum Disorders

In a 2017 diagnostic framework proposed by Castori and colleagues, the authors noted that while most cases of joint hypermobility are asymptomatic, some are associated with musculoskeletal symptoms/complications including dislocations, subluxations, chronic pain, and disturbed proprioception. For individuals with symptomatic joint hypermobility not having a well-defined syndrome such as hEDS, they proposed that the term "hypermobility spectrum disorder(s) (HSDs)" be used.[14]

In 2023, the International Consortium on EDS and HSD proposed that the 2017 International Criteria for hEDS not be used to establish the diagnosis in children. Instead, they recommended that children over the age of 5 be classified as having joint hypermobility when musculoskeletal complications are absent, or HSD when musculoskeletal complications are present. They developed a pediatric diagnostic framework that further categorizes hypermobile children based on their phenotypic and symptomatic presentation. This framework includes four components:[15]

- Generalized joint hypermobility (GJH)
- Skin and tissue abnormalities
- Musculoskeletal complications
- Core comorbidities (other features causing disability or distress, including chronic primary pain, chronic fatigue, functional gastrointestinal/bladder disorders, primary dysautonomia, and anxiety)

The above pediatric diagnostic framework was intended to be used after exclusion of other EDS types, HCTDs, genetic syndromes or neuromuscular disorders, until adulthood or biological maturity, at which point the 2017 International Criteria for hEDS should be used. Genetic testing was not recommended for all children with GJH, HSD, or hEDS.[15]

Test information

Clinical genetic testing is available for many HCTDs. Testing may include known familial mutation testing, next-generation sequencing, deletion/duplication analysis, or multigene panels.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

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Guidelines and evidence

Marfan Syndrome, Loeys-Dietz Syndrome, and TAAD

American College of Medical Genetics and Genomics

According to the American College of Medical Genetics and Genomics (ACMG, 2012) practice guidelines for the evaluation of Marfan syndrome (MFS):[26]

- "There is no case of classic, bona fide MFS due to mutations in a gene other than FBN1. However, current clinical molecular testing of FBN1 successfully detects mutations in such unequivocal patients in only about 90-95% of cases. For all of these reasons, searching for mutations in FBN1 continues to have a circumscribed role in the diagnosis of equivocal cases. Said differently, MFS remains, by and large, a clinical diagnosis."

American Heart Association

The American Heart Association (AHA, 2024) published a scientific statement on management of aortopathy in children and stated the following: [27]

- "The role of genetic testing for aortopathy has expanded with greater recognition of the importance of a specific genetic diagnosis in risk assessment as well as medical and surgical management. Genetic testing should be targeted to those with the highest likelihood of confirming a diagnosis and those for whom a genetic diagnosis would affect clinical management."
- "Multigene panels that include genes associated with HTAD [heritable thoracic aortic disease] are most commonly used; however, the genes included vary widely by laboratory. When there is a known familial pathogenic variant or when the clinical presentation strongly suggests a specific diagnosis, single gene testing can be used; for example, in the presence of ectopia lentis (lens dislocation), MFS [Marfan syndrome] associated with a variant in FBN1 is most likely. An HTAD panel may be considered for nonsyndromic presentations or in those with predominant systemic connective tissue findings. Broader testing (eg, whole exome sequencing) may be considered for early-onset and severe clinical presentations with features that are atypical for defined HTADs. Genetic testing should be initiated in the family member with the most severe and typical presentation."
- "Clinical diagnostic criteria for classic MFS have limitations in children. The MFS systemic score is a useful screening tool for historical and physical findings suggestive of MFS, but should not be relied upon in isolation."
- "Genetic testing should be performed in children suspected to have MFS; variants in FBN1 are found in >95% of children with MFS."

- "Absence of a positive genetic test result should not be assumed to rule out HTAD if clinical suspicion is otherwise high. Reclassification of uncertain variants, discovery of new genes, and addition of these genes to aortopathy panels occur on an ongoing basis. Thus, continued follow-up with genetics should be considered."

Indications for genetic testing in children with suspected HTAD included the following in the absence of bicuspid aortic valve (BAV):[27]

- "Personal history of aortic or arterial dissection/rupture, spontaneous bowel perforation
- Aortic root or ascending aortic Z score ≥2 and <3 and 1 or more features seen in syndrome HTAD without another non HTAD explanation
- Aortic root or ascending aortic Z score ≥3 OR dimension ≥4 cm without another non HTAD explanation
- Aortic root or ascending aorta ≥5 cm
- Multiple clinical features of syndromic HTAD (does not have to meet full clinical criteria)
- First degree family member with a (likely) pathogenic variant in HTAD gene
- First degree family member with history of aortic or arterial dissection/rupture, aortic aneurysm, bowel perforation"

Indications for genetic testing in children with BAV included:[27]

- "Personal history of aortic or arterial dissection/rupture, spontaneous bowel perforation
- Features seen in syndromic HTAD
- First degree family member with a (likely) pathogenic variant in HTAD gene
- First degree family member with history of aortic or arterial dissection/rupture, aortic aneurysm, bowel perforation

Consider when patient has BAV without the above but one of the following:

- Ascending aortic Z score ≥5.0
- Aortic root Z score ≥3.5
- Aortic root or ascending aorta ≥4 cm
- Aortic root phenotype (aortic root Z score > ascending aortic Z score)
- Family history of BAV, coarctation, HLHS (hypoplastic left heart syndrome)"

"Common non-HTAD associations with aortic root or ascending aortic Zscore ≥2 include congenital heart block; chronic renal disease and hypertension; certain congenital heart defects (ie, truncus arteriosus, dextro-transposition of the great arteries, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, single

ventricle status post Fontan); very low weight for height or age; or single or erroneous measurement."[27]

American Heart Association and American College of Cardiology

The American Heart Association (AHA, 2022) and American College of Cardiology (ACC, 2022) published clinical practice guidelines for the diagnosis and management of aortic disease. They stated the following regarding genetic evaluation and family screening:[18]

- Risk factors for familial thoracic aortic disease (TAD), also known as heritable thoracic aortic disease (HTAD), were outlined as:
  - "TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular EDS syndrome
  - TAD presenting at <60 years
  - A family history of either TAD or peripheral/intracranial aneurysms in a first- or second-degree relative
  - A history of unexplained sudden death at a relatively young age in a first- or second-degree relative"
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection, obtaining a multigenerational family history of TAD, unexplained sudden deaths, and peripheral and intracranial aneurysms is recommended."
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (ie, mutations) is recommended."
- "In patients with an established pathogenic or likely pathogenic variant in a gene predisposing to HTAD, it is recommended that genetic counseling be provided and the patient's clinical management be informed by the specific gene and variant in the gene."
- "In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (ie, cascade testing) is recommended. In family members who are found by genetic screening to have inherited the pathogenic/likely pathogenic variant, aortic imaging with TTE [transthoracic echocardiography] (if aortic root and ascending aorta are adequately visualized, otherwise with CT or MRI) is recommended."
- "In a family with aortic root/ascending aortic aneurysms or aortic dissection, if the disease-causing variant is not identified with genetic testing, screening aortic imaging of at-risk biological relatives (ie, cascade testing) is recommended."
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection, in the absence of either a known family history of TAD or pathogenic/likely pathogenic variant, screening aortic imaging of first-degree relatives is recommended."

- "In patients with acute type A aortic dissection, the diameter of the aortic root and ascending aorta should be recorded in the operative note and medical record to inform the management of affected relatives."
- "The HTAD genetic testing panels include (at the time of this writing) 11 genes that are confirmed to confer a highly penetrant risk for TAD: FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1. These panels also include genes that increase the risk for TAD and/or lead to systemic features that overlap with Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome. Clinical genetic testing is integral to the diagnostic evaluation of patients with TAD who have clinical indicators suggestive of an underlying single gene disorder. In patients who meet the clinical diagnostic criteria for Marfan syndrome but do not have ectopia lentis (ie, dislocated lens), genetic testing is reasonable to exclude an alternative diagnosis of Loeys-Dietz syndrome."

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (2014) stated the following:[28]

- "We recommend that surgical intervention be considered for thoracic aortic aneurysms according to the disease etiology and anatomic region affected… (Strong Recommendation, Moderate-Quality Evidence)."
- "We recommend clinical and genetic screening for suspected Marfan syndrome to clarify the nature of the disease and provide a basis for individual counseling (Strong recommendation, High quality evidence)"

"For non-Marfan, genetic forms of aortic disease:

- We recommend aortic imaging for first-degree relatives of patients with genetic forms of TAD to identify asymptomatic carriers (Strong Recommendation, Moderate-Quality Evidence).
- We recommend cardiac imaging in adult first-degree relatives of patients with BAV to identify asymptomatic carriers (Strong Recommendation, Moderate-Quality Evidence).
- We recommend screening for TAD-associated genes in non-BAV [bicuspid aortic valve] aortopathy index cases to clarify the origin of disease and improve clinical and genetic counseling (Strong Recommendation, Moderate Quality Evidence).
- We recommend that genetic counselling and testing be offered to first-degree relatives of patients in whom a causal mutation of a TAD-associated gene is identified. We recommend that aortic imaging be offered only to mutation carriers (Strong Recommendation, Low-Quality Evidence).
- We recommend complete aortic imaging at initial diagnosis and at 6 months for patients with LDS or a confirmed genetic aortopathy (e.g., TGFBR1/2, TGFB,

SMAD3, ACTA2, or MYH11) to establish if enlargement is occurring (Strong Recommendation, Moderate-Quality Evidence)."[28]

Cardiac Society of Australia and New Zealand

The Cardiac Society of Australia and New Zealand Cardiovascular Genetic Disease Council (CSANZ, 2017) stated:[29]

- "Molecular confirmation of a suspected clinical diagnosis is increasingly important for guiding patient management. As an example, an individual who looks marfanoid will have more extensive arterial imaging screening if identified to have a SMAD3 mutation as opposed to an FBN1 mutation."
- "A definitive molecular genetic diagnosis can clarify an equivocal clinical picture or result in a diagnosis in an apparently phenotypically normal individual. It is unknown at this stage what proportion of patients with these different genetic mutations will develop aortic dilatation or dissection. Identification of a causal mutation allows for the provision of accurate genetic counseling, the screening of at-risk family members and offers the possibility of accurate prenatal or preimplantation genetic diagnosis."
- "Sanger sequencing may be considered when there is no doubt about the clinical diagnosis. Despite clinical certainty however, a pathogenic mutation may not be found. Typically, exonic or whole-gene deletions and/or duplications are not detected by this method and require alternative technology e.g. quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes the relevant gene/chromosome segment."
- "Many clinical laboratories offer a multi-gene MFS/LDS/ familial TAAD panel that includes FBN1 and numerous other genes associated with aortic aneurysm and dissection disorders. This approach may be advantageous, given the known clinical and genetic heterogeneity of these disorders."
- "The clinical picture of non-syndromic aortopathies remains to be fully elucidated, and therefore the optimal extent and frequency of vascular imaging is unclear. We would err on the side of caution and suggest imaging the entire vasculature, at least at baseline, in non-syndromic individuals with a genetic mutation."
- "If there is a clear genetic diagnosis, then first-degree relatives should be offered predictive testing. If the screened relative does not have the familial mutation they can be released from screening. We advocate erring on the side of caution with respect to screening echocardiography of at-risk relatives." Screening was advised in the following relatives:
  1. "All family members who share the familial mutation and who therefore should be under clinical care, not screening"
  2. "At-risk family members where a clinical genetic diagnosis exists"

3. "At-risk family members where no clinical genetic diagnosis is made but the dissection occurred in a young individual without an apparent risk factor e.g. long standing hypertension"

European Reference Network on Rare Multisystemic Cardiovascular Diseases

The HTAD [heritable thoracic aortic disease] Rare Disease Working Group of the European Reference Network on Rare Multisystemic Cardiovascular Diseases (VASCERN, 2023) stated the following regarding genetic testing:[30]

"Genetic testing should be proposed when there is a high suspicion of an underlying genetic aortopathy and includes:

- patients with a familial form with or without hypertension (2 first or second-degree affected relatives) of thoracic aortic dissection or aneurysm (TAA/TAD),
- sporadic [defined as only one family member affected], TAA/TAD at
  - any age, in the absence of arterial hypertension, or
  - <70 years of age in presence of hypertension
- patients with non-traumatic ectopia lentis compatible with MFS
- patients with a combination of TAAD and syndromic features of Marfan or LDS."

"Nowadays, multiple genes are tested within panels dedicated to specific diseases. The genes tested may vary from one center to another but should include the following:

- ectopia lentis: FBN1
- TAA or TAD or systemic features: genes with a definitive or strong association with HTAD: ACTA2, COL3A1, FBN1, LOX, MYH11, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1, TGFBR2. This list is dynamic and will be updated regularly. The list of genes presently used in the various centers is available on the website of VASCERN."

"The technical capacity to detect small intragenic copy number variants using NGS data is suboptimal, though algorithms have improved considerably over the last few years.Additional high-resolution copy number variant analysis should be considered in case of negative panels in patients with a high suspicion. Furthermore, after multidisciplinary discussion, in some specific cases, it may be necessary to consider whole exome or genome sequencing for diagnosis since deep intronic variants can be present, or other syndromes, like Alagille syndrome, Noonan syndrome and neurofibromatosis type 1, can have TAA as a rare manifestation. Despite this, a causative variant remains unidentified in many (roughly 80%) non-syndromic HTAD patients."[30]

"In cases where the pathogenic variant is known, it is proposed that family members undergo genetic cascade screening. Thereafter, only patients carrying the pathogenic variant will need serial aortic imaging. When the disease-causing pathogenic variant

in the index patient is not known, follow-up by imaging (mainly TTE) of first-degree relatives depends on how many first or second-degree relatives have a dilated aorta."

- "In familial TAAs (at least 2 affected relatives), aortic imaging should be performed yearly when the aorta is dilated and every 5 years when aorta is not dilated in first-degree relatives."
- "In sporadic TAAs (only one family member affected), only the affected patient requires follow-up, and a single screening echocardiogram is deemed sufficient in adult relatives unless the first test is performed before the age of 40 years, in which case a further test after the age of 40 years could be considered. In case the measured aortic diameter is borderline, a second echocardiography after 5 years appears wise."[30]

European Society of Cardiology

The European Society of Cardiology (ESC, 2024) provided guidelines for the management of peripheral arterial and aortic diseases. Risk factors for HTAD were defined as the following:[31]

- In individuals with TAD ≤60 years of age:
  - Aortic dissection
  - Aortic dilatation in the absence of hypertension
  - Aortic dilatation with any additional risk feature (syndromic features of MFS, LDS, or vEDS and/or family history of TAD, peripheral/intracranial artery aneurysm, or unexplained sudden death at <60 years)
  - Aortic root/ascending z-score ≥3
- In individuals with TAD >60 years of age:
  - Aortic root/ascending z-score ≥3 or aortic dissection in the absence of hypertension
  - Aortic root/ascending z-score ≥3 or aortic dissection with any additional risk feature (syndromic features of MFS, LDS, or vEDS and/or family history of TAD, peripheral/intracranial artery aneurysm, or unexplained sudden death at <60 years)

The ESC provided the following recommendations regarding genetic testing and aortic imaging:[31]

- "In patients with aortic root/ascending aneurysms or thoracic aortic dissection and risk factors for HTAD, genetic counselling at an expert centre and subsequent testing, if indicated, is recommended." (Class I, Level B)
- "In patients with HTAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (i.e. cascade testing) is recommended, irrespective of age." (Class I, Level C)
- "In patients with HTAD, guidance of clinical management by the underlying gene/variant, when known, should be considered." (Class IIa, Level B)

- "In patients with TAD with risk factors for HTAD, with a negative family history of TAD and in whom no (likely) pathogenic variant is identified, TTE screening aortic imaging of FDRs [first-degree relatives] is recommended." (Class I, Level B)
- "Imaging screening of family members of patients with TAD with risk factors for HTAD in whom no (likely) pathogenic variant is identified should be considered starting at age 25, or 10 years below the youngest case, whichever is younger. If the initial screening is normal continued screening every 5 years until the age of 60 should be considered." (Class IIa, Level C)

European Society of Cardiology and European Society of Human Genetics

A consensus document for genetic counseling and testing in adults with congenital heart disease, published by the European Society of Cardiology (ESC, 2019) and European Society of Human Genetics (ESHG, 2019), recommended that genetic testing for HTAD include at least the genes known to have a "definitive" or "strong" association with the condition according to the Clinical Genome Resource (ClinGen) framework. Regarding when to test, the authors stated:[32]

- "…genetic testing may be considered after proper counselling and evaluation when at least two members of a family present HTAD or in isolated cases when (a) children (<18 years) present with aortic dissection or an aortic root diameter Z-score ≥3 or (b) adults present with aortic dissection or an aortic root diameter Z-score >3.5 or with a Z-score between 2.5–3.5 and <60 years or >60 years, and no arterial hypertension."

The ESC/ESHG, 2019 consensus document also addressed the relationship between BAV and TAAD:[32]

- "Familial occurrence of BAV has clearly been established with rates of 5–10% in first-degree relatives in various studies. Interestingly, the incidence of TAA in first-degree relatives is even higher in family members with TAV [tricuspid aortic valve] or BAV. The genetic basis of BAV is unclear. Rare pathogenic variants have been identified in a number of genes (SMAD6, NOTCH1, ROBO4, TBX20); however, these variants account for <5% of all BAV/TAA cases."
- "Echocardiographic screening in first-degree relatives of BAV patients is recommended and may be appropriate, particularly in boys, athletes and if hypertension is present. Genetic screening may be considered in familial cases with associated TAA."

National Working Group on Bicuspid Aortic Valve and Thoracic Aortic Aneurysm

A 2018 expert consensus recommendation published on behalf of the National Working Group on Bicuspid Aortic Valve (BAV) and Thoracic Aortic Aneurysm (TAA) stated the following regarding cardiogenetic care for individuals with thoracic aortic disease and their first-degree relatives:[33]

- High-risk groups for genetic predisposition are defined as thoracic aneurysm (equal to or greater than 45 mm) or dissection:
  - Age at diagnosis <50 years, or
  - Age at diagnosis 50-60 years, no hypertension, or
  - Positive family history, or
  - Syndromic features
- Due to the small size of modern families and reduced penetrance of hereditary thoracic aortic disease, the authors recommended the following:
  - "We suggest to define a positive family history as having at least one first- or second-degree relative with (1) a thoracic aortic aneurysm or dissection, (2) an aneurysm or dissection elsewhere in the arterial tree, diagnosed below 60#years of age, (3) a left-sided congenital heart defect (e.g. congenital aortic valve stenosis or bicuspid aortic valve) or patent ductus arteriosus, or (4) sudden death below 45#years of age."
- "In patients fulfilling the revised Ghent criteria for Marfan syndrome (e.g. combination of thoracic aortic disease with ectopia lentis), the probability of finding FBN1 mutation is high, between 66% and 91%. Therefore, targeted FBN1 analysis can be considered in these cases. If no specific syndromic features are present, next-generation sequencing (NGS) of multiple genes is the most efficient and cost-effective method."
- "If a disease-causing mutation has been identified in the proband, the working group recommends offering presymptomatic genetic testing to relatives. This is best undertaken using a stepwise approach called "cascade screening."
- Screening of first-degree relatives for familial TAA:
  - "Cardiovascular screening of mutation carriers should take place at or in close collaboration with an academic center, according to gene-specific management guidelines."
  - If no disease-causing mutation has been identified in the proband, screening should be offered to all first-degree relatives (parents, siblings, and children) starting at age 25 years or 10 years before the youngest case in the family using transthoracic echocardiography (TTE), baseline computed tomography (CT), or magnetic resonance imaging (MRI). If normal, repeat every 5 years. Discontinue at age 65 years or if first screening >60 years.

Selected Relevant Publications

In 1996, an international group of Marfan syndrome experts initially proposed clinical diagnostic criteria for Marfan syndrome called the Ghent nosology that gained wide acceptance.[34] The Ghent criteria were updated in 2010 and now address the role of FBN1 genetic testing in the diagnosis of Marfan syndrome.[22] While the authors did not make specific recommendations regarding when to perform genetic testing for Marfan syndrome, they did make the following statements:[22]

- "In practice, this does not make FBN1 testing a formal requirement (which imposes financial burden in some countries, and does not yet have 100% sensitivity and specificity), but allows its appropriate use when available."
- "The presence of aortic root dilatation (Z-score ≥2 when standardised to age and body size) or dissection and ectopia lentis allows the unequivocal diagnosis of MFS, irrespective of the presence or absence of systemic features except where these are indicative of SGS, LDS or vEDS."
- "Where aortic root dilatation (Z ≥2) or dissection is present but ectopia lentis is absent and the FBN1 status is either unknown or negative, an MFS diagnosis is confirmed by the presence of sufficient systemic findings (≥7 points, according to a new scoring system). However, features suggestive of SGS, LDS or vEDS must be excluded and appropriate alternative genetic testing (TGFBR1/2, collagen biochemistry, COL3A1, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed."
- "In the presence of ectopia lentis but absence of aortic root dilatation/dissection, the identification of an FBN1 mutation previously associated with aortic disease is required before making the diagnosis of MFS. If the FBN1 mutation is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as 'ectopia lentis syndrome'."

An expert-authored review for Marfan syndrome in 2022 noted that the condition can be confirmed in an individual meeting the Ghent criteria, and should be suspected in individuals with the following clinical findings:[6]

- Aortic root enlargement (z score ≥2.0)
- Ectopia lentis (diagnosed by slit-lamp examination after maximal pupillary dilation)
- A systemic score ≥7

When the clinical findings suggest the diagnosis of Marfan syndrome, recommended genetic testing approaches included single-gene analysis of FBN1, or a multigene Marfan syndrome / Loeys-Dietz syndrome / familial TAAD panel that includes FBN1.[6]

An expert-authored review in 2024 noted that no clinical diagnostic criteria have been published for Loeys-Dietz syndrome (LDS), but that the condition can be established in individuals with suggestive findings (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for specific examples).[7] The authors also stated, "The molecular diagnosis of LDS can be established in a proband who has a heterozygous pathogenic (or likely pathogenic) variant in SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, or TGFBR2 or biallelic pathogenic (or likely pathogenic) variants in IPO8 AND any of the following:

- Aortic root enlargement (defined as an aortic root z score ≥2 standard deviations above the mean) or type A dissection
- Other characteristic clinical features of LDS: craniofacial, skeletal, cutaneous, and/or vascular manifestations (especially arterial tortuosity, prominently including the

head and neck vessels, and aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree)
- Family history of established diagnosis of LDS"

For genetic testing to confirm a diagnosis of LDS, a multigene Marfan syndrome / Loeys-Dietz syndrome / familial TAAD panel that includes the above LDS genes, as well as other genes associated with TAAD, was recommended.[7]

An expert-authored review for vEDS recommended that genetic testing strategies include either single-gene testing of COL3A1, or a multigene panel including COL3A1 and other genes in the differential diagnosis (i.e. other EDS types, Marfan syndrome, LDS, or nsTAAD). The authors stated:[35]

- "No consensus clinical diagnostic criteria for vascular Ehlers-Danlos syndrome (vEDS) have been published. When the diagnosis is suspected on clinical grounds, molecular diagnostic testing of COL3A1 is indicated due to the presence of clinical phenocopies and variable expression of the vEDS phenotype. Criteria established in 2017 are useful to guide the approach to genetic testing."

EDS and Hypermobility Spectrum Disorders

International Consortium on the Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders

The International Consortium on the Ehlers-Danlos Syndromes (2017) developed clinical criteria for 13 recognized types of EDS as defined above in the "Diagnosis" section. The Consortium stated that genetic testing is needed to confirm the diagnosis when suspected based on clinical criteria (except for hEDS):[20]

- "In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other HCTDs, the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of (a) causative variant(s) in the respective gene."
- "Molecular diagnostic strategies should rely on NGS technologies, which offer the potential for parallel sequencing of multiple genes. Targeted resequencing of a panel of genes…is a time- and cost-effective approach for the molecular diagnosis of the genetically heterogeneous EDS. When no mutation (or in case of an autosomal recessive condition only one mutation) is identified, this approach should be complemented with a copy number variant (CNV) detection strategy to identify large deletions or duplications, for example Multiplex Ligation-dependent Probe Amplification (MLPA), qPCR, or targeted array analysis."
- "The diagnosis of hEDS remains clinical as there is yet no reliable or appreciable genetic etiology to test for in the vast majority of patients."

The International Consortium recommended that multigene panel testing include at least the gene(s) associated with the suspected EDS type. Broader panels were specifically suggested for kEDS, BCS, spEDS, and mcEDS due the phenotypic overlap between these types. Similarly, the authors suggested the inclusion of collagen type VI-related myopathies in multigene panel testing for suspected mEDS.[20]

In 2023, the Paediatric Working Group of the International Consortium on EDS and HSD developed a pediatric diagnostic framework that includes four components: generalized joint hypermobility (GJH), skin and tissue abnormalities, musculoskeletal complications, and core comorbidities. The framework supports categorization of hypermobile children into a group describing their phenotypic and symptomatic presentation. Regarding genetic testing, the authors stated:[15]

- "Hypermobility spectrum disorder is reserved for the combination of GJH and musculoskeletal symptoms, with the systemic subtype including those with both musculoskeletal symptoms and comorbidities. This can only be used after exclusion of other Ehlers–Danlos syndrome types, heritable disorders of connective tissue, syndromic conditions, chromosomal microdeletions, skeletal dysplasia, or neuromuscular disorders. This framework would not exclude the abovementioned diagnoses, and individual patients would need to be assessed for risk of alternate diagnosis and investigated appropriately, including, if indicated, next-generation sequencing (NGS) panel-based testing. Currently, we do not recommend genetic testing on all children with GJH, or HSD or hEDS. Medical specialists should remain guided by their clinical reasoning and the healthcare setting in which they practice when deciding if genetic testing is required."

Selected Relevant Publications

An expert-authored review by Zschocke and colleagues in 2024 summarized the genetic diagnosis of EDS. The authors noted that hEDS and HSD account for the majority of "suspected EDS" cases and emphasized that neither condition can be confirmed or excluded with genetic testing. A thorough clinical evaluation was recommended, followed by multigene panel testing for individuals suspected of having monogenic EDS (i.e. one of the 12 types for which the genetic etiology was known, which excluded hEDS/HSD):[5]

- "Diagnostic genetic testing is indicated in individuals with generalized joint hypermobility (with or without recurrent joint subluxations/dislocations) in conjunction with marked, typical skin manifestations (hyperextensibility, fragility, poor wound healing, atrophic scars, hemosiderosis etc.) and possibly arterial vascular events/organ rupture. In the absence of other pathognomonic skeletal, muscular, ocular, or oral manifestations, the genetic analyses may focus on the genes for type V, III and I collagen, TNXB, AEBP1, and ADAMTS2 (THBS2 unconfirmed)."

- "In the case of marked scoliosis and/or other skeletal deformities, myopathy, and marked neonatal muscular hypotonia, the analyses should cover PLOD1, FKBP14, B4GALT7, B3GALT6, B3GAT3, SLC39A13, CHST14, DSE and COL12A1. ZNF469 and PRDM5 should be targeted if brittle cornea syndrome is a possibility, whereas analysis of C1R and C1S is only necessary in the presence of typical oral manifestations. Special considerations may apply for infants or children in whom the clinical features may not yet be fully developed."
- "A broad massively parallel sequencing 'EDS panel' is sometimes recommended to exclude a genetic diagnosis in individuals with hypermobility even if there is no clear clinical suspicion of a monogenic disease. Although a pathogenic variant in one of the 'EDS genes' is sometimes identified in these cases, this non-specific approach may lead to an excess of expensive genetic investigations with unproven utility. It also has the risk of identifying potentially misleading variants of unknown significance (VUS) that may cause undue uncertainty and sometimes incorrect diagnoses, trigger unnecessary follow-up tests, and may lead to inadequate treatments."
- "Depending on health system resources, it is preferable to avoid genetic tests in suspected hEDS, or provide these to selected individuals that fulfill the strict 2017 hEDS criteria when the indication for testing is made by specialist clinical geneticists or rheumatologists with experience in diagnosing EDS. Vice versa, in the absence of pathognomonic monogenic EDS manifestations in individuals with hEDS/HSD, the latter diagnosis may be made based on the clinical assessment without the need to 'exclude' a monogenic EDS type."

Expert-authored reviews focused on hEDS/HSD likewise recommended that this EDS type be diagnosed clinically with the International Consortium criteria and indicated that genetic testing cannot be used to confirm the diagnosis. Rather, genetic testing should be guided by the presence of clinical history or physical examination findings that are concerning for other HCTDs.[24,36]

Stickler Syndrome

A 2020 review of Stickler syndrome (SS) by Boothe and colleagues noted that clinical diagnostic criteria were previously proposed for the condition but were not validated and may result in underdiagnosis of certain phenotypes. Instead, the authors recommended genetic testing to confirm the diagnosis:[21]

- "Molecular genetic testing should be pursued in any individual for whom SS is suspected. In addition to confirming a diagnosis in the individual, a molecular genetic diagnosis can assist in the testing of at-risk family members, in guiding medical management and screening and in providing accurate recurrence risk for offspring."
- "Many different approaches may be used when pursuing molecular genetic testing for SS. If family history and clinical findings are suggestive of a specific form of SS, one may consider obtaining single-gene testing. Likewise, if suspicion is high for

> AR SS, a gene panel analyzing only the genes associated with AR SS could be considered….[A]dvancements in next-generation gene sequencing technology, which utilizes methods that sequence millions of short-fragment DNA strands rapidly, allows for a cost-effective method for analyzing multiple genes at one time. Thus, one could initiate testing for all genes known to be associated with SS—COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, and COL9A3, rather than choose a sequential approach. This is often preferred because it leads to a more cost-effective and rapid diagnosis. If alternative diagnoses are being considered or if the phenotype is unclear, larger gene panels that include other genes or diagnoses of interest could be considered."

Another expert-authored review for Stickler syndrome in 2023 echoed the need for multigene panel testing to confirm the diagnosis in individuals with characteristic clinical features (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases*). In addition to the collagen genes related to Stickler syndrome, other genes associated with overlapping clinical phenotypes (e.g., BMP4, GZF1, LOXL3, LRP2, VCAN) may be included in multigene panel testing for this condition.[8]

A 2016 publication of consensus-derived best practices for Pierre Robin sequence (PRS) noted that Stickler syndrome is one of the most common genetic causes of this condition. As part of a comprehensive etiological assessment for PRS, the authors suggested genetic testing targeting the Stickler syndrome-associated collagen genes (COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3.[37] A 2024 consensus-based genetic testing algorithm for orofacial clefts similarly recommended that targeted testing for Stickler syndrome be considered for individuals with PRS.[38]

Other Hereditary Connective Tissue Disorders

There were limited clinical practice guidelines available for other HCTDs. A series of expert-authored reviews was published for arterial tortuosity syndrome, congenital contractural arachnodactyly, cutis laxa, FLNA deficiency, and Sphrintzen-Goldberg syndrome. Genetic testing was recommended, preferably via multigene panel, to confirm the diagnosis in individuals with characteristic features of these conditions (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases*).[9-13] The need for a multigene panel approach (i.e. cutis laxa or arteriopathy panel) was particularly emphasized for cutis laxa, and single-gene testing was described as "rarely useful and typically NOT recommended".[11]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary connective tissue and thoracic aortic disease genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate

diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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