Thoracic Aortic Aneurysms and Dissections (TAAD) Panel Genetic Testing

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Introduction

Thoracic aortic aneurysms and dissection (TAAD) panel 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 sequence analysis panel	81410
TAAD gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479

TAAD

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Procedures addressed by this guideline	Procedure codes
TAAD known familial mutation analysis	81403

Criteria

Introduction

Requests for thoracic aortic aneurysms and dissection (TAAD) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis for TAAD

- Genetic Counseling:
  - Pre- and post-test 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 Symptomatic or Presymptomatic Individuals:**
  - TAAD family mutation in 1st degree biological relative, AND
- Rendering laboratory is a qualified provider for service per the Health Plan policy.

****NOTE:** Since symptoms may occur in childhood, testing of children who are at-risk for a pathogenic mutation may be considered.

Sequencing Panel for TAAD

- Genetic Counseling:
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous panel testing for TAAD, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Cardiology examination consistent with a diagnosis of TAAD, and
  - Clinical features are not sufficiently specific to suggest a single condition, and
  - The results of the test will directly impact the diagnostic and treatment options that are recommended for the member, AND
- Rendering laboratory is a qualified provider for service per Health Plan policy.

Deletion/Duplication Analysis for TAAD

- Criteria for TAAD Genetic Testing Sequencing panel met, AND

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- No mutations found in TAAD Sequencing panel, AND
- No previous deletion/duplication analysis for TAAD, AND
- Rendering laboratory is a qualified provider for service per Health Plan policy.

Other Considerations

- This guideline addresses testing specifically for TAAD. For information on additional indications, please refer to the guideline *Hereditary Connective Tissue Disorder Testing*.
- For information on Marfan syndrome testing, please refer to the guideline *Marfan Syndrome Genetic Testing*, as this testing 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:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code.
    - Gene panels that are specific to TAAD that include the following genes will be eligible for reimbursement according to the criteria outlined in this guideline: FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK. This sequencing panel will only be considered for reimbursement when billed under an appropriate panel CPT code (e.g., 81410*).
    - Duplication/deletion panels will only be considered for reimbursement when billed under an appropriate panel CPT code (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.
  - When a TAAD multi-gene panel is billed with multiple stacked codes, only the following genes may be considered for reimbursement:

- TGFBR2
- TGFBR1
- ACTA2
- SMAD3

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*.

For general coding requirements, please refer to the guideline *Laboratory Billing and Reimbursement.*

What are thoracic aortic aneurysms and dissections (TAAD)?

The major cardiac problems seen in individuals with Thoracic Aortic Aneurysms and Dissections (TAAD) are aneurysm of the aorta, typically the aortic root and ascending aorta, and aortic dissections.[1]

Prevalence

Thoracic aortic aneurysm is seen in approximately 1% of the population.[2] In the absence of a known inherited syndrome, 20-30% of individuals with TAAD will have a positive family history.[1]

Symptoms

Most aneurysms are asymptomatic; however, If undetected and untreated, they can lead to aortic dissection, which is a life-threatening condition.[1,2] The individual's age at the time of aortic dissection and the severity of the disease can vary.[1]

Cause

To date, at least 37 genes have been identified in association with TAAD.[2] Some of these genes are associated with specific genetic conditions that may require additional management or surveillance. Medical management, including timing of surgery, may differ based on the underlying genetic etiology.[2-4] In many cases, a careful clinical examination by a specialist familiar with clinical features of these conditions can help to point toward one condition. In these cases, testing for gene(s) associated with a single condition would be most appropriate.

TAAD can be a symptom in several genetic syndromes, including:

- **Marfan syndrome (MFS)** – MFS is an autosomal dominant disorder that affects connective tissue in many parts of the body.[5] MFS is caused by mutations in the FBN1 gene. Diagnostic criteria, called the Ghent criteria, exists for Marfan syndrome. Major manifestations of the disease include aortic enlargement and ectopia lentis. Other features include, but are not limited to, bone overgrowth and joint laxity, long arms and legs, scoliosis, sternum deformity (pectus excavatum or carinatum), long thin fingers and toes, dural ectasia (stretching of the dural sac), hernias, stretch marks on the skin, and lung bullae. Symptoms can present in males or females at any age. Symptoms typically worsen over time. Infants who present with symptoms typically have the most severe disease course.[5]
- **Loeys-Dietz syndrome (LDS)** - LDS is an autosomal dominant disorder that affects many parts of the body.[6] LDS is mostly caused by mutations in either the TGFBR1 gene (20-25%) or TGFBR2 gene (55-60%). However, a small percentage of people with LDS may have mutations in SMAD2 (1-5%), SMAD3 (5-10%), TGFB2 (5-10%), or TGFB3 (1-5%). Major manifestations of this condition include "vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections), skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus, cervical spine malformation and/or instability), craniofacial features (widely spaced eyes, strabismus, bifid uvula/ cleft palate, and craniosynostosis that can involve any sutures), and cutaneous findings (velvety and translucent skin, easy bruising, and dystrophic scars)."[6] Given that there is no clinical diagnostic criteria established for LDS, genetic testing can help with the diagnosis.[6]
- **Vascular Ehlers-Danlos syndrome (vEDS or EDS type IV)** – EDS type IV is an autosomal dominant condition. It is caused by mutations in the COL3A1 gene. Major manifestations of this condition include "arterial, intestinal, and/or uterine fragility; thin, translucent skin; easy bruising; characteristic facial appearance (thin vermilion of the lips, micrognathia, narrow nose, prominent eyes); and an aged appearance to the extremities, particularly the hands."[7] Many adults present with the following symptoms: vascular dissection or rupture, gastrointestinal perforation, or organ rupture. Infants and children may present with congenital dislocation of the hips, clubfoot, pneumothorax, and/or recurrent joint subluxation or dislocation.[7]
- **Heritable Thoracic Aortic Disease (HTAD)** – HTAD describes those with TAAD who have absence of a known syndrome (e.g., Marfan syndrome, vEDS, LDS) and have a positive family history of TAAD.[1] 30% of those with HTAD will have a causative pathogenic variant identified in one of the known HTAD-related genes (including ACTA2, BGN, COL3A1, FBN1, FOXE3, LOX, MAT2A, MFAP5, MYH11, MYLK, PRKG1, TGFB2, TGFB3, TGFBR1, TGFBR2, SMAD3).[1,2]

Inheritance

Inherited forms of TAAD are most commonly autosomal dominant.[1] Not everyone who inherits a pathogenic variant in a gene associated with TAAD will develop an aortic aneurysm or dissection.

Autosomal recessive and X-linked patterns of inheritance have been reported for some associated genes.[2]

Diagnosis

TAAD can be diagnosed by various imaging studies, including echocardiography, computed tomography (CT) and MRI.[1] Genetic testing can be helpful to determine if there is an underlying genetic condition causing the TAAD.

Management

TAAD is managed with medications and regular imaging to assess the extent of aortic dilatation.[3] Surgical repair of the aorta may be necessary in some cases to help prevent aortic dissection.[1]

Survival

Survival depends on the occurrence of aortic dissection and the comorbidities that may be associated with an underlying genetic syndrome.

Test information

Introduction

Testing for TAAD may include known familial mutation analysis, next generation sequencing, deletion/duplication testing, and/or multigene panel testing.

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

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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.

The proportion of pathogenic TAAD mutations that are gene deletions or duplications is not well described.

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.

Many laboratories offer testing for at least 9 genes that have been associated with TAAD in their panels, including the genes that cause MFS, LDS, EDS type IV and HTAD. Detection rates of expanded panels vary by laboratory and depend on the genes included and the methods used for testing.[1]

Testing multiple genes, without supporting clinical features, has the potential to obtain results which may be hard to interpret. The chance that a variant of uncertain significance will be found increases as more genes are tested. However, given that many of the symptoms of conditions associated with TAAD overlap, if a person presents with overlapping features of more than one condition, a panel approach should be considered.

If features of a specific genetic disorder that is associated with TAAD are present, more targeted testing may be appropriate. For example, if an individual has TAAD and ectopia lentis, focused testing for Marfan syndrome (FBN1 sequencing and deletion/duplication analysis) is most appropriate.[1]

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Guidelines and evidence

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:[8]

- 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."

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (2014) stated the following:[9]

- "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 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)."
- "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)."

Cardiac Society of Australia and New Zealand

The Cardiac Society of Australia and New Zealand (CSANZ) Cardiovascular Genetic Disease Council (2017) stated:[10]

- "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."
- "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."
- "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 is 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 Society of Cardiology

The European Society of Cardiology (ESC, 2014) stated the following:[11]

- "Once a familial form of TAAD is highly suspected, it is recommended to refer the patient to a geneticist for family investigation and molecular testing." (Class I, Level C)

HTAD Rare Disease Working Group of VASCERN

The HTAD Rare Disease Working Group of VASCERN (2023) stated the following regarding genetic testing:[12]

"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."

"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."

If there is a high-degree of clinical suspicion, "high-resolution copy number variant analysis" may be indicated. In select, rare cases, whole exome or genome testing may considered.

In those with non-syndromic HTAD, a pathogenic mutation is not detected in roughly 80% of individuals.

If a pathogenic mutation is identified, genetic testing for at-risk family members is recommended. "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."

National Working Group on Bicuspid Aortic Valve and Thoracic Aortic Aneurysm

An 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:[13]

- 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
- "If no specific syndrome features are present, next-generation sequencing (NGS) of multiple genes (associated with TAA) 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.

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 thoracic aortic aneurysms and dissections (TAAD) panel 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 have the condition, but have non-standard features, will not receive an immediate approval for testing.

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