# Thoracic Aortic Aneurysms and Dissections (TAAD) Panel Testing

## 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.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA2 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>CBS Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>COL3A1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>COL5A1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>COL5A2 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>EFEMP2 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>FBN1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>MYH11 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>FBN2 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>FLNA Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>MED12 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>MYLK Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>NOTCH1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>PLOD1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>PRKG1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>SKI Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>SLC2A10 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>SMAD3 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>SMAD4 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
</tbody>
</table>
Procedures addressed by this guideline | Procedure codes
---|---
TGFB2 Known Familial Mutation Analysis | 81403
TGFB3 Known Familial Mutation Analysis | 81403
TGFBR1 Known Familial Mutation Analysis | 81403
TGFBR2 Known Familial Mutation Analysis | 81403
Aortic Dysfunction or Dilation Genomic Sequence Analysis Panel | 81410
Aortic Dysfunction or Dilation Duplication/Deletion Analysis Panel | 81411

What are thoracic aortic aneurysms and dissections (TAAD)

Definition

The major cardiac problems seen in individuals with Thoracic Aortic Aneurysms and Dissections (TAAD) include “dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta or both” \(^1\) and “dissections of the thoracic aorta involving either the ascending (Stanford type A dissections) or descending aorta (Stanford type B)” \(^1\) In some cases, vascular manifestations may be the only manifestation. \(^1\)

- TAAD can be diagnosed by various imaging studies, including echocardiography, computed tomography (CT), MRI, and angiography. \(^1\)
- The age of aortic dissection and the severity of the disease can range. \(^1\) Treatment for TAAD may involve medications. Surgical repair of the aorta may be necessary in some cases to help prevent aortic dissection. \(^1\)
- Cardiac problems seen with TAAD are associated with approximately 15,000 deaths every year. \(^1\)
- Genetic testing can be helpful to determine if there is an underlying genetic condition causing the TAAD. There are many genes which can predispose someone to TAAD. Some of these genes are associated with specific genetic conditions which may require additional management or surveillance. Medical management, including timing of surgery, may differ based on the underlying genetic etiology. \(^2,3\) 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.

- Specific genetic conditions that have TAAD as a clinical manifestation:
Marfan syndrome (MFS) – MFS is an autosomal dominant disorder that affects connective tissue in many parts of the body. MFS is caused by mutations in the FBN1 gene. Approximately 70-93% of people meeting diagnostic criteria for Marfan will have a mutation in this 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.

Loeys-Dietz syndrome (LDS) - LDS is an autosomal dominant disorder that affects many parts of the body. LDS is mostly caused by mutations in either the TGFBR1 gene (20%) or TGFBR2 gene (70%). However, a small percentage of people with LDS may have mutations in the SMAD3 gene (5%) or TGFB2 gene (1%). Major manifestations of this condition include “vascular findings (dilatation or dissection of the aorta, other arterial aneurysms or tortuosity), skeletal findings (pectus excavatum or pectus carinatum, scoliosis, joint laxity or contracture, long thin fingers and toes, cervical spine malformation and/or instability), craniofacial findings (widely spaced eyes, bifid uvula/cleft palate, craniosynostosis), and cutaneous findings (translucent skin, easy bruising, dystrophic scars).” Given that there is no clinical diagnostic criteria established for LDS, genetic testing can help with the diagnosis.

Ehlers-Danlos syndrome, Type IV (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 “thin, translucent skin; easy bruising; characteristic facial appearance (in some individuals); and arterial, intestinal, and/or uterine fragility.” 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, inguinal hernia, pneumothorax, and/or recurrent joint subluxation or dislocation.

Familial TAAD (TGFBR2, TGFBR1, MYH11, ACTA2, MYLK, and SMAD3) – Familial TAAD is diagnosed based on the following: “dilatation and/or dissection or the thoracic aorta, absence of clinical features of MFS, LDS or EDS Type IV, and a positive family history of TAAD.” Only 20% of people with a clinical diagnosis of Familial TAAD will have a mutation found in one of the above genes.

Test information

- 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
Familial TAAD. Detection rates of expanded panels vary by laboratory and depend on the genes included and the methods used for testing. In most cases, a careful and comprehensive clinical evaluation along with imaging studies will point to a specific diagnosis. Testing for conditions that are clinically indicated is the most appropriate place to start. 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 may be considered.

- Without symptoms of a specific genetic condition associated with TAAD, mutations in the ACTA2 gene are the most common. Mutations in this gene account for approximately 10-14% of Familial TAAD.
- Once a mutation is identified in a family member, the known familial mutation can be specifically identified in asymptomatic or symptomatic family members.

**Guidelines and evidence**

- Cardiac Society of Australia and New Zealand (CSANZ) Cardiovascular Genetic Disease Council (2017) states:
  - “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 counselling, 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:

i. “All family members who share the familial mutation and who therefore should be under clinical care, not screening”

ii. “At-risk family members where a clinical genetic diagnosis exists”

iii. “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.”

• The European Society of Cardiology (ESC, 2014) stated the following:¹⁸
  o “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)

• The Canadian Cardiovascular Society (2014) stated the following:⁹
  o “We recommend genetic screening for TAD-associated genes in non-BAV aortopathy index cases to clarify the origin of disease and improve clinical and genetic counselling (Strong recommendation, moderate quality evidence).”
  o “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).”
  o “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).”

  o Predictive genetic testing for at-risk relatives is addressed in the following guidelines statement:
    ▪ “If the mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging.” [Evidence level I: “Evidence from only expert opinion, case studies, or standard if care.” Recommendation classification C: “Recommendation that procedure or treatment is useful/effective.”]¹⁰
  o ACTA2 sequencing is addressed in the following guidelines statement:
“Sequencing of the ACTA2 gene is reasonable in patients with a family history of thoracic aortic aneurysms and/or dissections to determine if ACTA2 mutations are responsible for the inherited predisposition (Pannu et al., 2005; Guo et al., 2007; Zhu et al., 2006; Loeys et al., 2006; Stheneur et al., 2008; Guo et al., 2009).” [Evidence level IIa: “Only diverging expert opinion, case studies, or standard of care.” Recommendation classification B: “Recommendation in favor of treatment or procedure being useful/effective.”]⁹

- Additional genetic testing is addressed in the following guidelines statement:
  
  “Sequencing of other genes known to cause familial thoracic aortic aneurysms and/or dissection (TGFBR1, TGFBR2, MYH11) may be considered in patients with a family history and clinical features associated with mutations in these genes (Pannu et al., 2005; Guo et al., 2007; Zhu et al., 2006; Loeys et al., 2006; Stheneur et al., 2008; Guo et al., 2009).” [Evidence level IIb: “Greater conflicting evidence from single randomized trial or nonrandomized studies.” Recommendation classification B: “Recommendation's usefulness/efficacy less well established.”]⁹

- Patients with Loeys-Dietz syndrome or a confirmed genetic mutation known to predispose to aortic aneurysms and aortic dissections (TGFBR1, TGFBR2, FBN1, ACTA2, or MYH11) should undergo complete aortic imaging at initial diagnosis and 6 months thereafter to establish if enlargement is occurring. (Level of Evidence: C).”

Criteria

Known Familial Mutation(s) 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 for TAAD inclusive of known family 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.
TAAD Genetic Testing Sequencing Panel

Gene panels that are specific to TAAD that include the following genes will be eligible for coverage according to the criteria outlined in this policy: FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK. This sequencing panel will only be considered for coverage when billed under the appropriate panel CPT code: 81410. For criteria specific to Marfan syndrome, please see the policy *Marfan Syndrome Genetic Testing*.

- 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 patient, AND
- Rendering laboratory is a qualified provider for service per Health Plan policy

TAAD Genetic Testing Duplication/Deletion Panel

This duplication/deletion panel will only be considered for coverage when billed under the appropriate panel CPT code: 81411.

- Criteria for TAAD Genetic Testing Sequencing panel met, AND
- No mutations found in TAAD Sequencing panel, AND
- No previous deletion/duplication analysis for TAAD

Billing and reimbursement considerations

- This guideline addresses testing specifically for TAAD. Additional indications are addressed in the *Hereditary Connective Tissue Disorder Testing* guideline.
- When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to the panel code(s).
- If the laboratory will not accept redirection to a panel code, the medical necessity of 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
- MYH11
- ACTA2
- MYLK
- SMAD3

References


