Genetic Testing for Dilated Cardiomyopathy

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.

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What is Dilated Cardiomyopathy

Definition

Dilated cardiomyopathy is a heart condition characterized by an enlarged left ventricle and systolic dysfunction in the absence of coronary artery disease or other structural heart disease.

Incidence or prevalence

The best estimates of prevalence range from 1/250 to 1/1700. However, large scale studies have failed to determine accurate incidence or prevalence data given that DCM is likely underdiagnosed.
Symptoms

Average age of onset of DCM is in the 40s, but onset can begin as early as childhood. Enlargement of the left ventricle causes a weakened contraction of the heart muscle which in turn may lead to arrhythmias, including ventricular tachycardia or ventricular fibrillation, congestive heart failure, or thromboembolic disease.

Cause

Between 20 and 50% of idiopathic dilated cardiomyopathy (IDCM) cases are thought to have a genetic etiology.\(^1,2\) Approximately 35% of familial dilated cardiomyopathy cases are thought to have a genetic etiology.\(^1,2\)

Syndromic causes include muscular dystrophies such as Duchenne and Becker muscular dystrophy, limb girdle muscular dystrophy, myotonic dystrophy, facioscapulohumeral muscular dystrophy, Friedreich’s ataxia, and Emery-Dreifuss muscular dystrophy. Other syndromic causes include atypical Werner syndrome and Dunnigan-type familial partial lipodystrophy.

Non-genetic causes include infection, toxin exposure, metabolic disease, autoimmune disease, tachyarrythmia, sarcoidosis, and coronary artery disease.\(^3\)

Inheritance

Familial DCM can be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern, depending on the underlying syndrome or causative gene. While mitochondrial causes exist, they are exceedingly rare and often syndromic. Penetrance is reduced and age-dependent.\(^1,4\) Variable expressivity has also been noted.\(^1\) Several studies have identified 40 genes that are consistently linked to DCM.\(^1,3,5,6\)

A strong genotype-phenotype correlation exists for LMNA mutations resulting in high risk for sudden death and significant conduction system disease. As such, recommendations have been made for those harboring such a mutation to be restricted from competitive sports.\(^5\)

Diagnosis

Diagnosis of DCM can be established through echocardiogram or MRI to visualize left ventricular enlargement. Systolic dysfunction (ejection fraction below 50%) should be measured through 2D echocardiogram. While an ECG/EKG may be used as a screening tool to evaluate for hypertrophy, conduction abnormalities, and arrhythmias, it is not sufficient for a diagnosis of dilated cardiomyopathy.

A diagnosis of IDCM is given when syndromic genetic causes and non-genetic causes are ruled out.

Familial IDCM is diagnosed when two or more patients who are first or second degree relatives have individually met criteria for dilated cardiomyopathy. The presence of peripartum or pregnancy associated cardiomyopathy can be counted toward a
diagnosis of familial dilated cardiomyopathy when present in a relative of an affected individual.

Pre-symptomatic diagnosis of DCM has been shown to prevent symptoms and increase life expectancy. Therefore, screening with ECG and echocardiogram starting in childhood is recommended for first degree relatives of DCM patients without a clear etiology.\(^3\)

Evidence suggests testing symptomatic minors or testing minors for a known familial mutation can change their management and prevent sudden cardiac death.\(^5\)

**Treatment**

Early stages of DCM are often asymptomatic, but the natural history can be altered through treatment with reverse remodeling medications, pacemakers, or cardiac defibrillator device implantations. Severe or late stage disease otherwise refractory to these treatments is treated with heart transplant.\(^4\)

**Survival**

Survival depends on the etiology of DCM and whether the individual is symptomatic. In patients with heart failure, the survival is 20-30% eight years post-diagnosis.\(^7\)

**Test information**

**Introduction**

Testing for dilated cardiomyopathy may include known familial mutation analysis, single gene sequence analysis, deletion/duplication analysis, or multi-gene panels testing.

**Sequence analysis**

Until recently, most sequencing tests used the Sanger sequencing methodology that was originally developed in the 1970s. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.

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. NGS may not perform as well as Sanger sequencing in some applications.

NGS tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

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.

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.

Results may be obtained that cannot be adequately interpreted based on the current knowledge base. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.

Under certain circumstances, technologies used in multi-gene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion exists for a particular syndrome testing for that syndrome should be performed instead of a broad multi-gene panel.

Since genes can be easily added or removed from multi-gene tests over time by a given lab, medical records must document which genes were included in the specific multi-gene test used and in which labs they were performed.

Additionally, tests should be chosen to

- maximize the likelihood of identifying mutations in the genes of interest
- contribute to alterations in patient management
- minimize the chance of finding variants of uncertain clinical significance

**DCM Sequence Analysis**

The most common genetic causes of DCM include TTN, TNNT2, MYH7, MYH6, SCN5A, MYBPC3, and LMNA.\(^5,8\)

Larger panels may include genes that are considered rare causes of DCM. These include the following: ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CRYAB, CSRP3, DES, DMD, DSG2, EMD, EYA4, ILK, LAMP2, LDB3/ZASP, MYPN, NEBL, NEXN, PDLIM3, PLN, PSEN1, PSEN2, RBM20, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TPM1, TTR, TXNRD2, VCL.\(^5\)

Test yield has not been demonstrably higher when large scale testing is used versus disease specific panels.\(^9\)

No evidence exists to suggest testing of asymptomatic individuals when there is not a known familial mutation. This testing has not been shown to be effective due to the high volume of variants found with large cardiac panels. Instead, unaffected individuals with a suspicious family history should follow clinical monitoring guidelines.\(^5\)
Deletion/duplication analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, MLPA, and NGS data analysis.

These assays detect gains and losses too large to be identified through sequencing technology, often single or multiple exons or whole genes.

Known familial mutation analysis

Analysis for known familial mutations is typically performed by Sanger sequencing, but if available, a targeted mutation panel that includes the familial mutation may be performed.

Known familial mutations analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to DCM testing.

Heart Failure Society

The Heart Failure Society (2018) states:10

- “Guideline 4: Genetic testing is recommended for patients with cardiomyopathy (Level of evidence A)”
  - “4a: Genetic testing is recommended for the most clearly affected family member.”
  - “4b: Cascade genetic testing of at-risk family members if recommended for pathogenic and likely pathogenic variants.”
- “Genetic testing is recommended to determine if a pathogenic variant can be identified to facilitate patient management and family screening.”
- “Testing should ideally be initiated on the person in a family with the most definitive diagnosis and most severe manifestations. This approach would maximize the likelihood of obtaining diagnostic results and detecting whether multiple pathogenic variants may be present and contributing to variable disease expression or severity.”
- “Molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardio-vascular genetic medicine. Furthermore, multigene panel genetic testing is recommended over a serial single-gene testing
approach owing to the genetically heterogeneous nature of cardiomyopathy. Genetic testing and cascade screening have been shown to be cost-effective.”

- “In DCM, there is evidence for prognostication value of genetic testing and management implications for specific genetic findings, such as consideration of ICD placement for primary prevention in carriers of LMNA pathogenic variants.”

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2018) published a practice resource on genetic testing for cardiomyopathies. This practice resource is an abbreviated version of the Heart Failure Society Guidelines above, on which ACMG collaborated. They state the following.11,12

- “Recommendation 1. Genetic testing is recommended for patients with cardiomyopathy.”
- "(a) Genetic testing is recommended for the most clearly affected family member."
- "(b) Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants."
- "(c) In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered."

American College of Cardiology

The American College of Cardiology does not have specific testing guidelines. However, the following recommendations have been published in the Journal for the American College of Cardiology (2016):5

- Sequence analysis for disease specific gene panel is appropriate in an affected proband, regardless of family history.
- At risk relatives should be tested for pathogenic or likely pathogenic alterations identified in the proband.
- Testing of at risk relatives is not recommended if no mutation is identified in the proband. Instead, clinical monitoring is recommended.

Heart Rhythm Society and European Society of Cardiology

The Heart Rhythm Society and European Society of Cardiology (2011) states:13

- “Comprehensive or targeted (LMNA and SCN5A) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (i.e., first-, second-, or third-degree heart block) and/or a family history of premature unexpected sudden death.”
- “Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.”
• “Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.”
• Genetic testing is appropriate on post-mortem samples when there is sudden cardiac death.

Criteria

Introduction

Requests for DCM testing are reviewed using the following criteria.

Known Familial Mutation analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous full sequence testing or deletion/duplication analysis, and
  o Known disease-causing mutation in a DCM gene identified in 1st or 2nd degree relative(s), AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

Multi-Gene Panel Testing

• Genetic counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing
  o No previous full sequencing of requested genes, and
  o No known mutation identified by previous analysis, AND
• Diagnostic Testing for Symptomatic Individuals
  o Personal History
    ▪ Confirmed diagnosis of dilated cardiomyopathy by appropriate imaging and/or electrophysiology modality (e.g. echocardiogram, electrocardiogram, MRI, angiogram), and
• No evidence of a specific syndrome in patient or family, and
• Non-genetic causes such as infection, toxin exposure, and metabolic/autoimmune disease have been ruled out, OR
  o Personal & Family History Combination
    • A diagnosis of IDCM with one or more first or second degree relatives with a diagnosis of IDCM or peripartum cardiomyopathy, or
    • A diagnosis of IDCM with a suspicious family history including a first or second degree relative with sudden adult death or young cardiac or thromboembolic event, or
    • Mildly affected individual (defined as having dilated left ventricle but normal ejection fraction) with a first or second degree relative with a known diagnosis of IDCM who is deceased or otherwise unavailable for testing, AND

• Documentation from ordering provider indicating clear and specific impact result will have on medical care for the individual (e.g. change in surveillance or treatment plan), AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion/Duplication Analysis

• Genetic Counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o Member does not have a known mutation in a DCM gene, and
  o No previous deletion/duplication analysis for DCM genes, and
  o Meets criteria for full sequence analysis of DCM, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy

Billing and Reimbursement Considerations

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 the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement:
  - TTN
  - TNNT2
  - MYH7
  - MYH6
  - SCN5A
  - MYBPC3
  - LMNA

References

Introduction

This guideline cites the following references.


