Test Specific Guidelines

Dilated Cardiomyopathy Genetic Testing

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Introduction

Genetic testing for dilated cardiomyopathy is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
DCM Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
DCM Known Familial Mutation Analysis	81403
Hereditary Cardiomyopathy Panel (at least 5 cardiomyopathy-related genes)	81439

What Is Dilated Cardiomyopathy?

Definition

Dilated cardiomyopathy (DCM) 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.[1] Familial dilated cardiomyopathy is defined as the presence of 2 individuals within a family with DCM or a person with DCM and a first degree relative with sudden cardiac death (SCD) before age 35.[2-4] Dilated

cardiomyopathy is the leading cause of heart transplantation and accounts for 30-40% of congestive heart failure.[2] DCM is the third leading cause of heart failure in the United States.[5]

Prevalence

The best estimates of prevalence range from 1/250 to 1/1700.[2] However, large scale studies have failed to determine accurate prevalence data given that DCM is likely underdiagnosed.

Symptoms

Onset is usually in the fourth to sixth decade, but DCM can present at any age. 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.[3] Penetrance is reduced and age-dependent.[2,3] Variable expressivity has also been noted.[2]

Cause

Between 20 and 50% of idiopathic dilated cardiomyopathy (IDCM) cases are thought to have a genetic etiology. In the context of a family history, up to 35% of dilated cardiomyopathy cases are thought to have a genetic etiology.[2,6] Studies have identified more than 40 genes that are consistently linked to DCM.[1,2,7]

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.[8]

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.[3]

Diagnosis

The diagnosis of DCM can be established through echocardiogram or MRI to visualize left ventricular enlargement. Systolic dysfunction (ejection fraction below 45%) 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.[5,9]

Familial DCM is defined as the presence of 2 or more affected individuals with DCM within three generations or an individual with DCM and a relative with sudden unexplained death before age 35. Peripartum cardiomyopathy and myocarditis-associated cardiomyopathy have been seen in a familial setting.[9] The identification of a mutation in a disease causing gene can confirm familial DCM.

DCM sequencing panels vary by laboratory. The yield of testing is higher in individuals with a family history. Once a mutation is identified in a family member, targeted testing can be performed for the familial variant.[3] The most common genetic causes of DCM include TTN, TNNT2, MYH7, MYH6, SCN5A, MYBPC3, and LMNA.[1,7] LMNA and TTN are the most common causes, accounting for up to 26% of all mutations. These 7 genes in total account for up to 41% of mutations identified.[3]

Larger panels may include genes that are considered rare causes of DCM.[3] None of these rare genes alone contribute to more than 5% of mutations causing DCM.[3,10] Genes previously attributed to other cardiac diseases, such as hypertrophic cardiomyopathy or ARVC, have recently been implicated in DCM as well.[11] Phenotypes and initial clinical presentations can overlap.[3,11]

Test yield has not been demonstrably higher when large scale testing is used versus disease specific panels.[3,12]

Evidence suggests testing symptomatic minors or testing minors for a known familial mutation can change clinical management and prevent SCD.[1,13] A pre-symptomatic diagnosis of DCM has been shown to prevent symptoms and increase life expectancy. "It is appropriate to clarify the clinical and genetic status of asymptomatic family members at risk for DCM prior to the onset of manifestations to identify those with asymptomatic DCM and permit initiation of medical therapy aimed at preventing/delaying the morbidity of late-stage symptomatic disease."[3] Of note, ""…because multiple variants in DCM-associated genes have been observed in individuals with nonsyndromic DCM and because families may segregate pathogenic variants in more than one DCM-related gene, thorough individualized risk assessment through clinical, genetic, and family history analysis is warranted to determine if discharge from high-risk cardiac surveillance is appropriate" if an individual has a negative test for the familial variant.[3]

Screening with ECG and echocardiogram starting in childhood is recommended for first degree relatives of individuals with DCM without a clear etiology.[1,14] Genetic testing of asymptomatic individuals in the absence of a known familial mutation is not recommended.

Management

Early stages of DCM are often asymptomatic and 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 transplantation.[15] "In addition, identifying the probable cause of DCM helps tailor specific therapies to improve prognosis. An improved aetiology-driven personalized approach to clinical care will benefit patients with DCM, as will new diagnostic tools, such as serum biomarkers, that enable early diagnosis and treatment."[15]

A strong genotype-phenotype correlation exists for a subset of genes related to DCM. LMNA and SCN5A mutations result in high risk for SCD and significant conduction system disease. As such, recommendations have been made for those harboring such mutations to be restricted from competitive sports.[1,16] Preventive pacemakers or implantable cardioverter-defibrillators (ICD) may be considered in individuals with mutations in certain genes (such as LMNA, FLNC, DES, RBM20, PLN, DSP, DES, and EMD genes).[17]

Survival

Survival depends on the etiology of DCM and whether the individual is symptomatic. In individuals with heart failure, the survival is 20-30% eight years post-diagnosis.[5]

Test Information

Introduction

Testing for dilated cardiomyopathy may include known familial mutation analysis, next generation sequencing, deletion/duplication analysis, 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 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 patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and Evidence

Introduction

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

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 stated:[19]

“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."

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart

Rhythm Society, and Latin American Heart Rhythm Society

An expert consensus statement from the European Heart Rhythm Association, the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society and the Latin American Heart Rhythm Society (EHRA/HRS/APHR/LAHRS, 2022) addressed the utility and appropriateness of genetic testing for inherited cardiovascular conditions.[17] The consensus statements were categorized as follows:

Supported by strong observational evidence and authors' consensus

Some evidence and general agreement favor the usefulness/ efficacy of a test

There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing and variant interpretation:

Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]

If an individual has a clear phenotype, it is appropriate to analyze genes with definite/strong evidence support disease causation [Supported by strong observational evidence and authors' consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]

"Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multi-disciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists." Standard guidelines for variant interpretation should be used. Variant interpretation "can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration. [Supported by strong observational evidence and authors' consensus]

Variants of uncertain significance may be reclassified to likely pathogenic, pathogenic, likely benign or benign. [Some evidence and general agreement favor the usefulness/ efficacy of a test]

When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives can

be facilitated. [Supported by strong observational evidence and authors' consensus]

Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and authors' consensus]

Regarding genetic testing for DCM:

"Genetic testing is recommended for probands with DCM and family history of DCM, and the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN, DSP)." [Supported by strong observational evidence and authors' consensus]

"For genetic testing in a proband with DCM, the initial tier of genes tested may include genes with moderate evidence of pathogenicity (ACTC1, ACTN2, JPH2, NEXN, TNNI3, TPM1, VCL." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Genetic testing is recommended for patients with DCM and family history of premature unexpected sudden death or in a DCM patient with clinical features suggestive of a particular/rare genetic disease (such as atrioventricular block or sinus dysfunction or creatine phosphokinase elevation)." [Supported by strong observational evidence and authors' consensus]

"Genetic testing can be useful for patients with apparently sporadic DCM, particularly in the presence of either severe systolic dysfunction (left ventricular ejection fraction < 35%), or a malignant arrhythmia phenotype (e.g. sustained ventricular tachy- cardia/fibrillation), or particularly at a younger age." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Genetic testing may be considered for patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy)." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Genetic testing is useful for patients with DCM to improve risk stratification and guide therapy." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

"Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant." [Supported by strong observational evidence and authors' consensus]

"Predictive genetic testing in related children is recommended in those aged >10-12 years." [Supported by strong observational evidence and authors' consensus]
"Predictive genetic testing in related children aged below 10-12 years may be considered, especially where there is a family history of early-onset disease." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

Heart Failure Society of America

The Heart Failure Society of America (HFSA, 2018) stated:[13]

"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."

"4c: In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered."

"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."

National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand

The National Heart Foundation of Australia (NHFA, 2018) and Cardiac Society of Australia and New Zealand (CSANZ, 2018) stated:[20]

"Genetic testing may be considered in patients with dilated cardiomyopathy (DCM) associated with conduction disease, for prognostic stratification and to guide management regarding the use of implantable cardioverter debrillators."

Criteria

Introduction

Requests for DCM testing are reviewed using the following criteria.

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

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:

Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing

No previous full sequencing of requested genes, and

No known mutation identified by previous analysis, AND

Diagnostic Testing for Symptomatic Individuals

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 the individual or family, and

Non-genetic causes such as infection, toxin exposure, metabolic disease, autoimmune disease, tachyarrythmia, sarcoidosis, and coronary artery disease have been ruled out, OR

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:

Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

Member does not have a known mutation in a DCM gene, and

No previous deletion/duplication analysis for DCM genes, and

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

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