Introduction

Dilated cardiomyopathy is a condition in which the left ventricle (the main pumping chamber of the heart) becomes enlarged and can no longer pump effectively. This can lead to heart failure, as well as cause an abnormal rhythm of the heart. It has been found that sometimes dilated cardiomyopathy seems to run in families, and in these cases it may be caused by a genetic problem. Doing genetic tests to see if a genetic problem has caused a person’s dilated cardiomyopathy is still investigational. Testing people who do not have any known heart problems to see if they are at risk for developing dilated cardiomyopathy is also investigational. Medical studies have not shown that this type of testing helps to manage the care of patients. For this reason, genetic testing for dilated cardiomyopathy is still considered to be unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Testing

<table>
<thead>
<tr>
<th>Genetic testing for dilated cardiomyopathy</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing for dilated cardiomyopathy is considered investigational in all situations.</td>
<td></td>
</tr>
</tbody>
</table>

Coding

There are several listings of genetic tests performed for dilated cardiomyopathy in the CPT Tier 2 molecular pathology codes listed below.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td></td>
<td>–Includes: PLN (phospholamban) (eg, dilated cardiomyopathy, hypertrophic cardiomyopathy), full gene sequence</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td></td>
<td>–Includes: ANKRD1 (ankyrin repeat domain 1) (eg, dilated cardiomyopathy), full gene sequence; TPM1 (tropomyosin 1 [alpha]) (eg, familial hypertrophic cardiomyopathy), full gene sequence; TNNC1 (troponin C type 1 [slow]) (eg, hypertrophic cardiomyopathy or dilated cardiomyopathy), full gene sequence</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td></td>
<td>–Includes: LDB3 (LIM domain binding 3) (eg, familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence; LMNA (lamin A/C) (eg, Emery-Dreifuss muscular dystrophy; [EDMD1, 2 and 3] limb-girdle muscular dystrophy; [LGMD] type 1B, dilated cardiomyopathy; [CMD1A], familial partial lipodystrophy; [FPLD2]), full gene sequence; TNNT2 (troponin T, type 2 [cardiac]) (eg, familial hypertrophic cardiomyopathy), full gene sequence</td>
</tr>
<tr>
<td>81407</td>
<td>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt;50 exons, sequence</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>analysis of multiple genes on one platform)</td>
</tr>
<tr>
<td></td>
<td>–Includes: MYH6 (myosin, heavy chain 6, cardiac muscle, alpha) (eg, familial dilated cardiomyopathy), full gene sequence; MYH7 (myosin, heavy chain 7, cardiac muscle, beta) (eg, familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence; SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (eg, familial dilated cardiomyopathy), full gene sequence</td>
</tr>
<tr>
<td>81439</td>
<td>Inherited cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTN</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

If a genetic sequencing panel (GSP) is performed that does not meet the criteria in code 81439, the relevant tier 2 codes above would be reported for the specific genes tested, and the unlisted molecular pathology code would be reported 1 time for the remaining genes in the panel that lack a specific CPT.

**Related Information**

**Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.
Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Description

Dilated cardiomyopathy (DCM) is characterized by progressive left ventricular enlargement and systolic dysfunction, leading to clinical manifestations of heart failure. There are a variety of causes of DCM, including genetic and nongenetic conditions. Genetic forms of DCM are heterogeneous in their molecular basis and clinical expression. Genetic testing for DCM has potential utility in confirming a diagnosis of genetic DCM, and as a prognostic test in family members when familial DCM is present.

Background

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is defined as the presence of left ventricular enlargement and dilatation in conjunction with significant systolic dysfunction. DCM has an estimated prevalence of 1 in 2700 in the United States.\(^1\) The age of onset for DCM is variable, ranging from infancy to the eighth decade, with most individuals developing symptoms in the fourth through sixth decades.\(^2\)

Diagnosis

Primary clinical manifestations of DCM are heart failure and arrhythmias. Symptoms of heart failure, such as dyspnea on exertion and peripheral edema, are the most common presentation of DCM. These symptoms are generally gradual in onset and slowly progressive over time. Progressive myocardial dysfunction also may lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope, or sudden cardiac arrest.

Many underlying conditions can cause DCM, including\(^3\):

- Ischemic coronary artery disease
- Toxins
- Metabolic conditions
- Endocrine disorders
- Inflammatory and infectious diseases
- Infiltrative disorders
- Tachycardia-mediated cardiomyopathy

Therefore, when a patient presents with DCM, a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. Extensive workup including cardiac magnetic resonance imaging, exercise testing, right-sided catheterization with biopsy, and 24-hour ECG monitoring will uncover only a small number of additional etiologies for DCM.\(^4\) Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for secondary causes.\(^3\) This has traditionally been termed idiopathic dilated cardiomyopathy (IDC).

Clustering of IDC within families has been reported, leading to the conclusion that at least some cases of DCM have a genetic basis. Familial DCM is diagnosed when 2 closely related family members have IDC in the absence of underlying causes. Penetrance of familial DCM is variable and age-dependent, often leading to lack of appreciation of the familial component.

**Treatment**

Treatment of DCM is similar to that for other causes of heart failure. This includes medications to reduce fluid overload and relieve strain on the heart, and lifestyle modifications such as salt restriction. Patients with clinically significant arrhythmias also may be treated with antiarrhythmic medications, pacemaker implantation, and/or an automatic implantable cardiac defibrillator. Automatic implantable cardiac defibrillator placement for primary prevention also may be performed if criteria for low ejection fraction and/or other clinical symptoms are present. End-stage DCM can be treated with cardiac transplantation.

**Genetic DCM**

Genetic DCM has been proposed as a newer classification that includes both familial DCM and some cases of sporadic IDC. The percentage of patients with sporadic DCM that has a genetic basis is not well characterized. Most disease-associated variants are inherited in an autosomal dominant fashion, but some autosomal recessive, X-linked, and mitochondrial patterns of inheritance also are present.\(^5\)

In general, genotype-phenotype correlations are either not present or not well-characterized. There have been some purported correlations between certain disease-associated variants and
the presence of arrhythmias. For example, patients with conduction system disease and/or a family history of sudden cardiac death may be more likely to have disease-associated variants in the LMNA, SCN5A, and DES genes. Kayvanpour et al (2017) performed a meta-analysis of genotype-phenotype associations in DCM. The analysis included 48 studies (total N=8097 patients) and found a higher prevalence of sudden cardiac death, cardiac transplantation, and ventricular arrhythmias in LMNA and PLN disease-associated variant carriers and increasing penetrance with age of DCM phenotype in subjects with TTN-truncating variants.

There may be interactions between genetic and environmental factors that lead to the clinical manifestations of DCM. A genetic variant may not in itself be sufficient to cause DCM, but may predispose to developing DCM in the presence of environmental factors such as nutritional deficiencies or viral infections. It also has been suggested that DCM genetics may be more complex than simply single-gene variants, with low-penetrance variants that are common in the population contributing to a cumulative risk of DCM that includes both genetic and environmental factors.

**Genetic Testing for DCM**

Approximately 30% to 40% of patients referred for genetic testing will have a disease-associated variant identified. Disease-associated variants linked to DCM have been identified in more than 40 genes of various types and locations. The most common genes involved are those that code for titin (TTN), myosin heavy chain (MYH7), troponin T (TNNT2), and alpha-tropomyosin (TPM1). These 4 genes account for approximately 30% of disease-associated variants identified in cohorts of patients with DCM. A high proportion of the identified disease-associated variants are rare, or novel, variants, thus creating challenges in assigning the pathogenicity of discovered variants. Some individuals with DCM will have more than 1 DCM-associated variant. The frequency of multiple disease-associated variants is uncertain, as is the clinical significance.

**Summary of Evidence**

For individuals who have signs and/or symptoms of dilated cardiomyopathy (DCM) who receive comprehensive genetic testing, the evidence includes case series reporting clinical validity. Relevant outcomes are overall survival, test accuracy and validity, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. There is a large degree of uncertainty with clinical validity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 50%. Clinical specificity of DCM-associated variants is unknown, but DCM-associated variants in the same
genes have been reported in 1% to 3% of patients without DCM. Because of the suboptimal clinical validity, the accuracy of assigning variants as disease-associated or benign may also be suboptimal. The clinical usefulness of genetic testing for diagnosing DCM has not been demonstrated. For a patient who is diagnosed with idiopathic DCM, the presence of a DCM-associated variant will not change treatment or prognosis. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who are asymptomatic with a first-degree relative who has DCM and a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes case series reporting test accuracy and clinical value. Relevant outcomes are test accuracy and validity, symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. For an individual at risk due to genetic DCM in the family, genetic testing can identify whether a familial variant has been inherited. However, it is uncertain how knowledge of a familial variant improves outcomes for an asymptomatic individual. The uncertain clinical validity of predictive testing makes it unclear whether actions taken as a result of testing will improve outcomes. Early treatment based on a genetic diagnosis is unproven. The evidence is insufficient to determine the effect of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed below.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02148926</td>
<td>Clinical and Genetic Examinations of Dilated Cardiomyopathy</td>
<td>480</td>
<td>Sep 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT01736566</td>
<td>The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine</td>
<td>220</td>
<td>Aug 2017 (ongoing)</td>
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<tr>
<td>NCT01857856</td>
<td>PHOspolamban RElated CARDiomyopathy STudy - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)</td>
<td>150</td>
<td>Apr 2020</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02057341</td>
<td>A Study of ARRY-371797 in Patients With LMNA-Related</td>
<td>12</td>
<td>May 2016</td>
</tr>
</tbody>
</table>
Practice Guidelines and Position Statements

**British Society of Echocardiography**

Guidelines from the British Society of Echocardiography (2017) have presented diagnostic criteria for assessing dilated cardiomyopathy (DCM) with echocardiography, recommending that caregivers regularly administer echocardiograms to individuals with potential genetic risk, particularly those related to an individual with idiopathic DCM. The guidelines did not address the use of genetic testing in cases of DCM.

**Cardiac Society of Australia and New Zealand**

The Cardiac Society of Australia and New Zealand published a 2017 position statement on the appropriate assessment of and treatment for familial DCM. The statement addressed the growing number of potentially pathogenic novel variants, recommending that any genetic tests be evaluated by experts in molecular cardiology to prevent unnecessary or inaccurate reporting to family members should the variant in question not be disease-causing. The authors recommended genetic testing for individuals related to patients with familial DCM, especially relatives of young patients. In general, individuals with increased risk of familial DCM (eg, women of child-bearing age, families with a history of conduction system disease) should be counseled on lifestyle modification and followed at regular intervals.

**Heart Rhythm Society and European Hearth Rhythm Association**

The Heart Rhythm Society and European Hearth Rhythm Association issued joint guidelines (2011) on genetic testing for cardiac channelopathies and cardiomyopathies. These guidelines contained the following recommendations on genetic testing for DCM:

**Class I recommendations**
“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 with a family history of premature unexpected sudden death.”

“Mutation-specific testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation [variant] in the index case.”

Class IIa recommendations

“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.”

The Heart Rhythm Society and European Heart Rhythm Association (2011) consensus statement also noted that prophylactic implantable cardioverter defibrillator can be considered in patients with known arrhythmia and/or conduction system disease (LMNA or Desmin [DES]).

Heart Failure Society of America

The Heart Failure Society of America published practice guidelines (2009) on the genetic evaluation of cardiomyopathy. The following recommendations for genetic testing for cardiomyopathy (including DCM) were made:

“Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered (Level of Evidence B).”

“Genetic testing should be considered for the one most clearly affected person in a family to facilitate screening and management.”

“Genetic and family counseling is recommended for all patients and families with cardiomyopathy (Level of Evidence A).”

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for cardiomyopathy have been identified.
Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


55. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011;8(8):1308-1339. PMID 21787999

**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>03/10/14</td>
<td>New Policy. New policy developed with literature review through December 15, 2013. Genetic testing for dilated cardiomyopathy is considered investigational for all indications.</td>
</tr>
<tr>
<td>07/24/14</td>
<td>Update Related Policies. Remove 12.04.91.</td>
</tr>
<tr>
<td>03/10/15</td>
<td>Annual Review. Policy updated with literature review through December 23, 2014; references 5, 18-19, and 21-25 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Annual Review, approved March 8, 2016. Policy updated with literature review through November 17, 2015; reference 1 updated; references 4 and 24 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Coding update; added new CPT code 81439 effective 1/1/17.</td>
</tr>
<tr>
<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. Policy updated with literature review through December 21, 2016; references 6-10, 18-21, 26-27, and 39-43 added. The policy is revised with updated genetics nomenclature – mutation changed to variant when applicable. Policy statement unchanged.</td>
</tr>
<tr>
<td>09/22/17</td>
<td>Policy moved to new format, no changes to policy statement.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through December 2017; references 29, 33-34, and 46-54 added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.
Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Premera Blue Cross (TTY: 800-842-5357) at 800-722-1471 (TTY: 800-842-5357).