Policy Statement

Genetic testing for dilated cardiomyopathy is considered investigative in all situations.

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO) 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 PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

### Table PG1. 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</td>
<td>Disease-associated variant identified in a proband for use in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

### Table PG2. 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</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>significance</td>
<td></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.

Coding

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

Code **81403** (Molecular Pathology Procedure Level 4) includes:
2.04.114  Genetic Testing for Dilated Cardiomyopathy
Page 2 of 21

- PLN (phospholamban) (e.g., dilated cardiomyopathy, hypertrophic cardiomyopathy), full gene sequence

Code **81405** (Molecular Pathology Procedure Level 6) includes:
- ANKRD1 (ankyrin repeat domain 1) (e.g., dilated cardiomyopathy), full gene sequence
- TPM1 (tropomyosin 1 [alpha]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
- TNNC1 (troponin C type 1 [slow]) (e.g., hypertrophic cardiomyopathy or dilated cardiomyopathy), full gene sequence

Code **81406** (Molecular Pathology Procedure Level 7) includes:
- LDB3 (LIM domain binding 3) (e.g., familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence
- LMNA (lamin A/C) (e.g., 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
- TNN2 (troponin T, type 2 [cardiac]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence

Code **81407** (Molecular Pathology Procedure Level 8) includes:
- MYH6 (myosin, heavy chain 6, cardiac muscle, alpha) (e.g., familial dilated cardiomyopathy), full gene sequence
- MYH7 (myosin, heavy chain 7, cardiac muscle, beta) (e.g., familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence
- SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (e.g., familial dilated cardiomyopathy), full gene sequence

The following genomic sequencing panel (GSP) CPT code is specific for inherited cardiomyopathy testing:
- **81439**: Inherited cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)

If a genomic sequencing panel 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 81479 would be reported 1 time for the remaining genes in the panel that have not been codified by CPT.

### 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 for confirming a diagnosis of genetic DCM and as a prognostic test in family members when familial DCM is present.

### Related Policies

- General Approach to Evaluating the Utility of Genetic Panels
- Genetic Testing for Cardiac Ion Channelopathies
- Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy
Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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.

Rationale

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 varies, 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 electrocardiography 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 two 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.

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 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.

**Literature Review**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms are better when the test is used to manage the condition than when another test or no test is used to manage the condition.
The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Testing Patients with Signs and/or Symptoms of Dilated Cardiomyopathy**

Clinical Context and Test Purpose

The purpose of genetic testing in patients who have signs and/or symptoms of dilated cardiomyopathy (DCM) is to confirm a diagnosis and inform treatment decisions such as the decision on when to implant a cardioverter defibrillator. Because DCM presents with nonspecific symptoms and can be caused by various disorders, it has been proposed that genetic testing can confirm a DCM diagnosis in borderline cases or idiopathic DCM. Decisions on medical therapy in symptomatic DCM patients are generally based on cardiac phenotype, although the prophylactic placement of a pacemaker and/or implantable cardioverter defibrillator is sometimes considered in patients with DCM and LMNA or desmin (DES) disease-associated variants.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with signs and/or symptoms of DCM?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is patients with signs and/or symptoms of DCM (i.e., heart failure or arrhythmias, frequently presenting as dyspnea on exertion and peripheral edema), which is considered idiopathic DCM after a negative workup for secondary causes.

**Interventions**

Genetic testing can be performed on any number of candidate genes, individually or collectively. Lists of genes that may lead to inherited cardiomyopathies and testing laboratories in the United States are provided at the GeneTests website funded by BioReference Laboratories and the Genetic Testing Registry of the National Center for Biotechnology Information website. Because of a large number of potential variants associated with DCM and the infrequent nature of most variants, panel testing is frequently offered. Examples of commercially available genetic panels for DCM are listed in Table 1.

**Table 1. Commercially Available Genetic Panels for DCM**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>No. of Genes Tested</th>
<th>Testing Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambry Genetics</td>
<td>DCMNext panel</td>
<td>36</td>
<td>NGS</td>
</tr>
<tr>
<td></td>
<td>CardioNexta</td>
<td>84</td>
<td>NGS/Sanger sequencing</td>
</tr>
<tr>
<td>GeneDX</td>
<td>DCM/Left Ventricular Non-Compaction Panel</td>
<td>61</td>
<td>CGH/NGS</td>
</tr>
<tr>
<td></td>
<td>Combined Cardiac Panelb</td>
<td>120</td>
<td>CGH/NGS</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy Panel</td>
<td>91</td>
<td>CGH/NGS</td>
</tr>
<tr>
<td>Partners Healthcare</td>
<td>DCM/Arrhythmogenic Cardiomyopathy Panel</td>
<td>53</td>
<td>NGS</td>
</tr>
<tr>
<td></td>
<td>Pan Cardiomyopathy Panelb</td>
<td>62</td>
<td>NGS</td>
</tr>
<tr>
<td>Baylor COM</td>
<td>DCM panel</td>
<td>52</td>
<td>NGS</td>
</tr>
<tr>
<td>Invitae</td>
<td>Primary DCM panel</td>
<td>69</td>
<td>NGS</td>
</tr>
<tr>
<td></td>
<td>Add-on Preliminary-evidence Genes</td>
<td>22</td>
<td>NGS</td>
</tr>
<tr>
<td></td>
<td>Add-on Autosomal Recessive Syndromic Pediatric Cardiomyopathy Genes</td>
<td>6</td>
<td>NGS</td>
</tr>
</tbody>
</table>
Comparators
The comparator of interest is standard clinical care without genetic testing such that decisions regarding medical therapy in symptomatic DCM patients are being made based on cardiac phenotype.

Outcomes
Specific outcomes are listed in Table 2.

Table 2. Outcomes of Interest for Individuals with Symptomatic Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>2-year survival</td>
</tr>
<tr>
<td>Change in disease status</td>
<td>New York Heart Association heart failure class</td>
</tr>
<tr>
<td>Symptoms</td>
<td>KCCQ or other validated symptom assessment tools</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>KCCQ; timed walk; exercise testing</td>
</tr>
<tr>
<td>QOL</td>
<td>KCCQ, Minnesota Living with Heart Failure or other validated QOL assessment tools</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Adverse events of implantable cardioverter defibrillator</td>
</tr>
</tbody>
</table>

KCCQ: Kansas City Cardiomyopathy Questionnaire; QOL: quality of life.

The potentially beneficial outcomes of primary interest would be an improvement in overall survival and change in disease status because changes in management in symptomatic DCM are initiated to prevent sudden cardiac death and slow or reverse the progression of heart failure. Improvement in symptoms, functioning, and quality of life are also important.

The potentially harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse events from that treatment, in this case, placement of an implantable cardioverter defibrillator.

Timing
Trials of genetic testing or treatment strategies in this population were not found. Two trials of implantable cardioverter defibrillator use in other nonischemic cardiomyopathies have reported that changes in 2- and 5-year overall survival are meaningful for interventions for cardiomyopathies. Therefore, 2-year survival and changes in other outcomes over the same period should be considered meaningful in this review.

Setting
Patients may be referred from primary care to a cardiologist for investigation and management of idiopathic DCM. Evaluation and genetic testing of cardiomyopathy are complex. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:
- Technically reliable
- Clinically valid
- Clinically useful
Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer either to predicting a future condition or to predicting a response to therapy.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Numerous studies have evaluated the proportion of patients with clinically diagnosed DCM who have disease-associated variants. These studies vary in the genes examined and methods used to detect these variants. A common type of study describes the presence of 1 type of disease-associated variants in probands with DCM or family members of the proband. Fewer studies have evaluated multiple genes in cohorts of patients with DCM. In addition, only a limited number of studies have used next-generation sequencing (NGS), which is expected to have higher sensitivity than other methods and also is expected to have higher rates of variants of uncertain significance.

**Next-Generation Sequencing**
The studies evaluating multiple genes using NGS or whole-exome sequencing are summarized in Table 3 and explained in more detail below.

### Table 3. Studies Evaluating the Clinical Validity of Genetic Testing for DCM Using NGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sequencing Method</th>
<th>Genes Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haas et al (2015) [23]; INHERITANCE</td>
<td>639 patients with sporadic (51%) or familial (49%) DCM</td>
<td>NGS</td>
<td>84 genes</td>
<td>- Known DCM-causing variants found in 101 (16%) patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Likely pathogenic variants found in 147 (23%) patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- More than 1 DCM-associated variants in 82 (13%) patients</td>
</tr>
<tr>
<td>Dalin et al (2017) [24]</td>
<td>176 unrelated patients with idiopathic DCM and 503 healthy reference individuals from European ancestry cohort</td>
<td>NGS</td>
<td>41 DCM-related genes</td>
<td>- 55 (31%) patients had 1 variant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 24 (14%) patients had ≥2 variants</td>
</tr>
<tr>
<td>Pugh et al (2014) [25]</td>
<td>766 patient with idiopathic DCM</td>
<td>NGS</td>
<td>Panels ranging from 5-46 genes</td>
<td>- Clinical sensitivity increased from 10% to 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Inconclusive cases increased from 5% to 51%</td>
</tr>
</tbody>
</table>
DCM: dilated cardiomyopathy; NGS: next-generation sequencing.

The largest study to date, the European INHERITANCE (INtegrated HEart Research In TrANSlational genetics of dilated Cardiomyopathies in Europe) project, examined a comprehensive set of disease-associated variants and used NGS as the testing method. A total of 639 patients with sporadic (51%) or familial (49%) DCM were enrolled in 8 clinical centers in Europe between 2009 and 2011. Secondary DCM was ruled out by excluding patients with hypertension, valve disease, and other loading conditions; coronary artery disease was ruled out by coronary angiography in 53% of patients. NGS was used to sequence 84 genes. Pathogenicity of variants was classified as known (included in the Human Genome Mutation Database for heart muscle diseases and channelopathies); likely (frameshift insertions or deletions, stop-gain or stop-loss variants, and splice-site variants); potential (not common, nonsynonymous variants associated with “disease” prediction according to online calculator, SNPs&GO); or benign (identified in the SNP database with allele frequency ≥1%). Known DCM-associated variants were found in 101 (16%) patients, most commonly in the PKP2, MYBPC3, and DSP genes. Additionally, 117 likely pathogenic variants were found in 26 genes in 147 (23%) patients, most commonly in TTN, PKP2, MYBPC3, DSP, RYR2, DSC2, DSG2, and SCN5A. Eighty-two (13%) patients carried more than 1 DCM-associated variant, and there was considerable overlap of identified disease-causing variants with other cardiac diseases: 31% of patients had variants associated with arrhythmogenic right ventricular cardiomyopathy; 16% with hypertrophic cardiomyopathy; 6% with channelopathies; and 6% with other cardiac diseases.

Dalin et al (2017) used NGS to sequence the coding regions of 41 DCM-associated genes in 176 unrelated patients with idiopathic DCM, and they were compared with 503 healthy reference individuals in the European ancestry cohort of the 1000 Genomes project. Fifty-five (31%) patients had 1 variant in the analyzed genes, and 24 (14%) patients had 2 or more variants. Genetic variants in any gene, or variants in LMNA, MYH7, or TTN alone, were all associated with early disease onset and reduced transplant-free survival. LMNA variants had the strongest association with transplant-free survival. There was no difference in the prevalence of familial DCM between patients with and without variants. Patients with more than 1 variant were more likely to have familial DCM or potential familial DCM compared with patients with only 1 variant (p=0.046). Stop-gain and frameshift variants were more common in DCM patients (12%) than in the healthy reference individuals (0.6%). However, the prevalence of missense variants was 35% DCM patients and 37% healthy reference individuals; conservation and pathogenicity scores and localization of missense variants were also similar in the 2 groups.

Pugh et al (2014) used NGS to test gene panels of increasing size, ranging from 5 to 46 genes, in 766 DCM patients tested over 5 years at a single molecular diagnostics laboratory. For calculating clinical sensitivity, “positive” cases were those with variants of known, likely, or strongly suspected clinical significance. The clinical sensitivity increased from 10% to 37% as gene panel sizes increased and likewise the number of inconclusive cases also increased from 5% to 51%. No “positive” variants were found in 24 of 46 tested genes. The clinical sensitivity for patients with a family history of DCM was similar to that of the entire cohort. TTN was the largest contributor to positive test results (14%); LMNA and MYH7 each contributed about 5%.

**Other Sequencing Methods**

Hirtle-Lewis et al (2013) used whole-exome sequencing of 4 genes as part of a strategy to identify and classify genetic variants associated with DCM. The population comprised 96 patients with idiopathic DCM treated at a Canadian clinic. The 4 genes examined were LMNA, TNNI2, TCAP, and PLN, all of which had been previously examined by direct-sequence analysis without any disease-associated variants identified. Eleven variants were identified, seven of which were novel. Two variants were judged to have a high probability of causing disease, four were judged to be variants of uncertain significance (VUS), with the remainder considered benign.
In 2017, van der Linde et al published a retrospective analysis of 80 individuals (15 probands, 65 family members) in the Netherlands who had a variant in the \textit{MYH7} gene identified through whole exome sequencing.\textsuperscript{29} Cardiomyopathy was observed in 47.7\% of individuals with the variant gene, and the majority (63\%) of those with cardiomyopathy also showed a reduced left ventricular ejection fraction. A higher proportion of individuals with the variant gene had a congenital heart defect compared with the likelihood observed in the general Dutch population (8.8\% vs 1\%). Following haplotype analysis, the investigators concluded that the variant observed appeared to be a founder mutation in \textit{MYH7}, acknowledging that the sample size and length of follow-up were not optimal and could not account for other potential genetic factors.

The remaining studies have used older testing methods or examined only a subset of genes known to contain DCM-associated variants; a representative sample of these studies is described below. Hershberger et al (2008) examined a cohort of 313 patients with DCM, 183 with familial DCM, and 130 with sporadic DCM.\textsuperscript{30} Thirty-one unique variants were identified in 36 (11.5\%) probands. The 6 genes evaluated (and the frequencies of disease-associated variants identified) were: \textit{MYH7} (4.2\%), \textit{TNNT2} (2.9\%), \textit{SCN5A} (2.6\%), \textit{TCAP} (1.0\%), \textit{LDB3} (1.0\%), and \textit{CSRP3} (0.3\%). However, only 11 of the 31 probands had variants judged to be probably pathogenic. The remainder were judged to be possibly (n=21) or unlikely (n=4) pathogenic.

Millat et al (2011) examined a cohort of 105 unrelated patients with DCM.\textsuperscript{31} Sixty-four individuals had familial DCM, and 41 had sporadic DCM. All coding exons and intronic junctions of the \textit{MYH7}, \textit{LMNA}, \textit{TNNT2}, \textit{TNNI3}, and \textit{RBM20} genes were examined by high-resolution melting and direct sequencing. Pathogenic variants were found in 19\% (20/105) of individuals. Ten pathogenic variants were novel variants, and nine were previously described variants.

Lakdawala et al (2012) studied 264 unrelated adult and children with DCM, approximately half of whom had familial disease.\textsuperscript{32} Ten genes (\textit{MYH7}, \textit{TNNT2}, \textit{TNNI3}, \textit{TPM1}, \textit{MYBPC3}, \textit{ACTC}, \textit{LMNA}, \textit{PLN}, \textit{Taz}, \textit{LDB3}) were analyzed by direct-sequence. Forty unique pathogenic variants were identified in 17.4\% (46/264) individuals with DCM. Genes with the most frequent pathogenic variants were \textit{MYH7} (6.6\%), \textit{LMNA} (5.3\%), and \textit{TNNT2} (3.7\%). VUS were identified in an additional 10.6\% (28/264) of individuals.

In an observational study, Hasselberg et al (2017) followed 79 individuals with a lamin A/C variant (\textit{LMNA}) and either symptomatic (n=48) or asymptomatic familial DCM (n=31) who were referred to a single center in Norway for genetic testing as either probands or family members.\textsuperscript{33} Initially, the investigators identified 561 probands with familial DCM, and only 6.2\% (n=35) of these had the \textit{LMNA} variant. Given the combined likelihood of mortality, the requirement for heart transplantation (24\%) and the considerable frequency of other cardiac events observed during follow-up in both symptomatic and asymptomatic groups, the investigators recommended that relatives of probands with known \textit{LMNA} variant be screened due to increased risk.

A small Slovakian study by Priganc et al (2017) screened 58 patients with DCM or hypertrophic cardiomyopathy for variants in exons 12, 20, or 21 of \textit{SCN5A} gene; also included were 26 healthy individuals.\textsuperscript{34} Of the 10 missense variants found, three were judged to be pathogenic (T12471, A1260D, G1262S); however, given that the incidence of the variants was mixed between case and control cohorts, there was no clear association between disease and the presence of a variant. Roughly one-third (32.76\%) of the patients with DCM or hypertrophic cardiomyopathy did not show any variant in the \textit{SCN5A} gene; this result and the small size of the study made conclusions uncertain.

A few studies have documented the range of diagnoses (i.e., lack of specificity) associated with DCM-associated variants. In the Netherlands, the \textit{PLN} (phospholamban) R14del variant is a founder mutation present in 10\% to 15\% of patients diagnosed with DCM or arrhythmogenic right ventricular cardiomyopathy/dysplasia. In a 2014 retrospective study of 295 symptomatic and asymptomatic \textit{PLN} R14del variant carriers, 21\% of patients met diagnostic criteria for DCM.\textsuperscript{35} In
another 2014 retrospective cohort of 41 symptomatic and asymptomatic LMNA variant carriers, 32% were diagnosed with DCM.36

Section Summary: Clinically Valid
There is a large degree of uncertainty about the clinical validity of genetic testing for DCM. Clinical sensitivity is likely to be low, in the range of 10% to 50%. A minority of patients will have multiple DCM-associated variants, and these patients are likely to have the more severe disease. New DCM-associated variants continue to be discovered. A substantial number of DCM patients will have variants associated with other cardiomyopathies. It is unclear whether these represent phenotypic variability from a single variant, or whether these variants are not causative of DCM. Clinical specificity also is uncertain; variants thought to be pathogenic have been reported in some patients without cardiomyopathy.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The potential clinical usefulness of genetic testing for DCM includes confirmation of the diagnosis, evaluating whether there is a genetic cause in an individual with idiopathic DCM, and/or evaluating whether a close relative has inherited a disease-causing variant known to be present in the family.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing would be clinically useful if it could confirm the diagnosis of DCM when the diagnosis cannot be made clinically, or if it were used to confirm a diagnosis earlier than would otherwise be possible without genetic testing, and if earlier diagnosis led to management changes that improve outcomes.

The diagnosis of DCM is made on clinical grounds, requiring the presence of left ventricular enlargement and evidence of systolic dysfunction. The presence or absence of a disease-associated variant will not alter the clinical diagnosis of DCM. Genetic testing may influence the diagnostic workup for the underlying etiology of DCM. In patients with a likely familial component, genetic testing may improve the efficiency of workup by avoiding other tests for secondary causes of DCM likely to be negative.37 However, many of these tests (i.e., testing for thyroid disease, diabetes, and echocardiography) are simple and noninvasive. Coronary angiography to rule out coronary artery disease still may be necessary for patients with a DCM-associated variant, depending on age and other risk factors for coronary artery disease. Therefore, the impact of genetic testing on the efficiency of workup is unknown. In patients with sporadic forms of DCM, testing for secondary causes will likely still precede genetic testing, so that genetic testing will not influence the diagnostic workup. Current treatment for DCM does not vary according to whether a disease-associated variant is present.37

Although researchers have investigated pharmacogenetic associations in DCM, the absence of prospective, randomized trials to compare standard treatment with genotype-guided treatment precludes the findings being clinically useful. Reddy et al (2015) evaluated the impact of adrenergic receptor genotype on hemodynamic status in 2 cohorts of pediatric patients (age
<22 years) who had DCM and stable (n=44) or advanced (i.e., listed for transplantation; n=91) heart failure. Three adrenergic receptor variants associated with heart failure in adults were genotyped: ADRA2C del322-325, ADRB1 Gly389Arg, and ADRB2 Gly16Arg. At mean follow-up of 2.2 years, patients with stable or advanced heart disease who had at least 1 variant showed greater response to β-blocker treatment than patients who had no variant (genotype × β-blocker interaction p values ≤0.05 for several hemodynamic parameters). Wasielewski et al (2014) reported on a descriptive study investigating whether familial DCM may predispose to anthracycline-associated cardiomyopathy. Genotyping of 48 cardiomyopathy-associated genes in patients with DCM who also had anthracycline-associated cardiomyopathy (n=5) and in patients with anthracycline-associated cardiomyopathy alone who met criteria for familial DCM based on family history (n=6) identified 2 known pathogenic variants and 9 VUS.

Section Summary: Clinically Useful
Genetic testing for DCM has not been established as clinically useful. Genetic testing is not likely to alter the diagnosis of DCM, which is based on clinical factors. Studies of pharmacogenetic associations to guide treatment selection in DCM are preliminary and do not permit conclusions about whether management decisions were changed based on genetic testing. Predictive testing may lead to changes in surveillance, but testing is currently limited by low clinical validity and heterogeneity in penetrance and clinical expression of disease.

Testing Asymptomatic Individuals to Determine Future Risk
Clinical Context and Test Purpose
The purpose of genetic testing for patients who are asymptomatic with a close relative who has DCM and a known genetic variant is to inform decisions regarding the frequency of screening and timing of initiation of treatment such as when to implant a cardioverter defibrillator or start therapy with β-blockers or angiotensin-converting enzyme inhibitors.

It has been proposed that early initiation of therapy with angiotensin-converting enzyme inhibitors or β-blockers may slow progression of heart failure, but there is no evidence to support their use in asymptomatic patients.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals who are asymptomatic with a close relative who has DCM and a known disease-associated variant?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals who are asymptomatic with a close relative who has DCM and a known pathogenic variant.

Interventions
The genetic testing for DCM is performed using tests that should be primarily focused on the variant(s) identified in the relative with DCM.

Comparators
The comparator of interest is standard clinical care without genetic testing such that decisions on screening and medical therapy are based on guidelines for patients with a relative with DCM.

Outcomes
Specific outcomes are listed in Table 4.

The potentially beneficial outcome of primary interest would be a reduction in the incidence of morbid events because changes in management in symptomatic DCM are initiated to prevent...
the development of heart failure and tachycardia. Prevention of symptoms, maintenance of function, and quality of life are also important.

The potentially harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse events from that treatment, in this case, placement of implantable cardioverter defibrillator or treatment with angiotensin-converting enzyme inhibitors or β-blockers. False-negative test results could lead to delay in diagnosis and treatment.

Table 4. Outcomes of Interest for Asymptomatic Individuals with a Relative with DCM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbid events</td>
<td>Incidence of heart failure or tachycardia</td>
</tr>
<tr>
<td>Symptoms</td>
<td>KCCQ or other validated symptom assessment tools</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>KCCQ; timed walk; exercise testing</td>
</tr>
<tr>
<td>QOL</td>
<td>KCCQ, Minnesota Living with Heart Failure or other validated QOL assessment tools</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Adverse effects of ICD, ACE inhibitors, or β-blockers</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme; DCM: dilated cardiomyopathy; ICD: implantable cardioverter defibrillator; KCCQ: Kansas City Cardiomyopathy Questionnaire; QOL: quality of life.

Timing
The appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, and children) and variation in age of onset of DCM from genetic causes. Changes in outcomes due to increased screening or early initiation of treatment in asymptomatic patients would take years to become evident. Ten-year differences in the incidence of morbid events or other outcomes would be considered meaningful for this review.

Setting
Family members of individuals diagnosed with DCM may be referred to a secondary or tertiary care setting for clinical screening and genetic testing. Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Several studies have described the prevalence of DCM in family members of patients diagnosed with idiopathic DCM, with estimates ranging from 20% to 35%. However, studies on the yield of targeted genetic testing in family members are limited. Brodt et al (2013) evaluated 103 family members of patients with DCM from 16 pedigrees previously identified to carry LMNA familial variants. Sixty-four (62%) family members carried their familial LMNA variant, and 51 (79%) of those had electrocardiographic abnormalities at initial screening (mean age of onset, 41 years; range, 18-76 years). Twenty-six (25%) had ventricular dysfunction (mean age of onset, 48 years; range, 28-82 years), and 11 (11%) had DCM. Sixteen family members with electrocardiographic abnormalities at initial screening later developed DCM; the electrocardiographic abnormalities preceded DCM by a median of 7 years.

Gene identification technologies have increased the number of DCM-associated novel variants, but the prevalence and clinical significance remain indeterminate (see Table 5).
Table 5. Familial Studies and Case Reports of DCM-Associated Novel Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sequencing Type</th>
<th>Gene Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernlund et al (2017)45</td>
<td>11-mo proband with DCM and 6 family members</td>
<td>NGS</td>
<td>TNNT2, BAG3</td>
<td>• 4 individuals had TNNT2-variant; 2 had TNNT2 and BAG3 variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Onset and severity of disease varied</td>
</tr>
<tr>
<td>Asadi et al (2017)46</td>
<td>6 members of a family with history of CHF</td>
<td>NGS</td>
<td>δ-Sg</td>
<td>2 individuals had a heterozygous variant (p.R97Q) in δ-Sg gene; the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>variant was not found in 100 controls</td>
</tr>
<tr>
<td>Bodian et al (2017)47</td>
<td>Infant proband with intractable diarrhea and DCM</td>
<td>WGS</td>
<td>EPCAM</td>
<td>The EPCAM-variant (c.556-14A&gt;G) suggests intestinal tufting, but this</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>condition was not observed</td>
</tr>
<tr>
<td>Yuan et al (2017)48</td>
<td>Proband and 4 family members with DCM and/or</td>
<td>WES</td>
<td>KCNJ 12</td>
<td>Of 12 shared variants identified, the KCNJ 12 variant (p.Glu334del) did</td>
</tr>
<tr>
<td></td>
<td>arrhythmia</td>
<td></td>
<td></td>
<td>not appear in European or African registries</td>
</tr>
<tr>
<td>Petropoulou et al (2017)49</td>
<td>Proband and 1 family member with atypical DCM</td>
<td>WES</td>
<td>TNNT2, MYH7</td>
<td>Variants found (c.247A&gt;C; p.Asn83His in TNNT2; c.2863G&gt;A; p.Asp955Asn in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MYH7) were assessed as potentially damaging or disease-causing; a third</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>variant in PRDM16 was inconclusively associated with cardiomyopathy</td>
</tr>
<tr>
<td>Rafiq et al (2017)50</td>
<td>3 members of a family with history of DCM</td>
<td>WES</td>
<td>BAG 3</td>
<td>• 4 other members were described but not tested</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Tested individuals showed BAG 3 variant (Chr10:121435979-delC)</td>
</tr>
<tr>
<td>Liu et al (2017)51</td>
<td>• Family 1: proband and 5 family members with DCM</td>
<td>WES</td>
<td>TTN</td>
<td>Family 1: Nonsense variant (c.12325C&gt;T/p.R4109X) assessed as disease-</td>
</tr>
<tr>
<td></td>
<td>• Family 2: asymptomatic proband and 4 family</td>
<td></td>
<td></td>
<td>causing and - damaging</td>
</tr>
<tr>
<td></td>
<td>members with DCM</td>
<td></td>
<td></td>
<td>Family 2: Missense variant (c.17755G.C/p.G5919R) absent in control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cohort</td>
</tr>
</tbody>
</table>

CHF: congestive heart failure; DCM: dilated cardiomyopathy; NGS: next-generation sequencing; WES: whole-exome sequencing; WGS: whole-genome sequencing.

**Section Summary: Clinically Valid**

The evidence for clinical validity of genetic testing for DCM in asymptomatic persons who are relatives of a person diagnosed with idiopathic DCM is limited to case series and reports describing the prevalence of the most common genetic variants or the yield of targeted testing. Gene identification technologies have increased the number of DCM-associated novel variants, but the prevalence and clinical significance remain indeterminate.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

In family members of patients with DCM, genetic testing can be used to determine whether a known pathogenic variant has been inherited. Several issues in predictive testing for DCM create challenges for establishing that genetic testing is clinically useful.

This first requires confidence that the variant identified in the proband causes DCM (clinically valid). If there is uncertainty about the pathogenicity of the variant, then genetic testing may provide misleading information. Because of the high number of novel variants and VUS identified...
in DCM, the confidence that a variant causes the disorder is less than for many other cardiac conditions.

Uncertain penetrance and variable clinical expression also need to be considered in determining the utility of predictive testing.\textsuperscript{37} Because of heterogeneity in clinical expression, it may not be possible to adequately counsel an asymptomatic patient on the precise likelihood of developing DCM, even when an inherited variant has been identified.

Predictive testing may lead to changes in screening and surveillance, particularly for patients who test negative in whom surveillance might be discontinued.\textsuperscript{37} However, it is uncertain whether this approach leads to improved outcomes because of the uncertain clinical validity of testing. For example, a proband may be identified with a variant that is possibly pathogenic. A close family member may test negative for that variant and be falsely reassured that they are not at risk for DCM when they still may have another undiscovered variant.

Current surveillance and early treatment for DCM does not vary based on the presence or absence of a disease-associated variant.\textsuperscript{37,52} While there is general agreement that early treatment for DCM is optimal, no trials demonstrated improved outcomes with presymptomatic treatment compared with delaying treatment until the onset of symptoms, although at least one such trial is in progress (see Ongoing and Unpublished Clinical Trials section). A multicenter European RCT (NCT01583114) had planned to analyze the impact of ACE inhibitors in subjects who carry a variant but had not yet developed DCM was terminated due to inadequate enrollment. If early treatment is based primarily on genetic testing, then additional concerns of false-positive (initiating unnecessary treatment and adverse events of those treatments) and false-negative test results (delay of treatment initiation) need to be considered.

\textbf{Section Summary: Clinically Useful}

There is no direct or indirect evidence that knowledge of a specific familial variant improves outcomes for asymptomatic individuals. Clinical guidelines supporting increased surveillance apply to individuals with a close family member regardless of genetic testing. Initiation of treatment is based on clinical findings. Early treatment based on a genetic diagnosis is unproven.

\textbf{Summary of Evidence}

For individuals who have signs and/or symptoms of 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 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.

**Supplemental Information**

**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.\(^5^3\) 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.\(^5^4\) 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 (e.g., 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 Heart Rhythm Association**
The Heart Rhythm Society and European Heart Rhythm Association issued joint guidelines (2011) on genetic testing for cardiac channelopathies and cardiomyopathies.\(^5^5\) These guidelines included following recommendations on genetic testing for DCM (see Table 6).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>“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.”</td>
<td>I</td>
</tr>
<tr>
<td>“Mutation-specific [familial variant] testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.”</td>
<td>I</td>
</tr>
<tr>
<td>“Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.”</td>
<td>Ila</td>
</tr>
</tbody>
</table>

COR: class of recommendation; DCM: dilated cardiomyopathy.

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]).\(^5^5\)

**Heart Failure Society of America**
The Heart Failure Society of America published practice guidelines (2009) on the genetic evaluation of cardiomyopathy.\(^5^2\) 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
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 7.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</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>
</tr>
<tr>
<td>NCT01857856</td>
<td>PHOsholamban RElated CARDiomyopathy Study - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)</td>
<td>150</td>
<td>Apr 2020</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02057341a</td>
<td>A Study of ARRY-371797 in Patients With LMNA-Related Dilated Cardiomyopathy</td>
<td>12</td>
<td>May 2016 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

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


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (e.g., 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>CPT®</td>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>CPT®</td>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (e.g., 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>CPT®</td>
<td>81407</td>
<td>Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt;50 exons, sequence analysis of multiple genes on one platform)</td>
</tr>
<tr>
<td>CPT®</td>
<td>81439</td>
<td>Hereditary cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include</td>
</tr>
</tbody>
</table>
2.04.114 Genetic Testing for Dilated Cardiomyopathy

Page 20 of 21

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN) (Code revision effective 1/1/2018)</td>
</tr>
<tr>
<td>81479</td>
<td></td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
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<td>ICD-10</td>
<td>None</td>
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<tr>
<td>Procedure</td>
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</tbody>
</table>

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2017</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>04/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>04/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence.
over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.