2.04.114 Genetic Testing for Idiopathic Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Original Policy Date:</th>
<th>April 30, 2015</th>
<th>Effective Date:</th>
<th>July 1, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section:</td>
<td>2.0 Medicine</td>
<td>Page:</td>
<td>Page 1 of 21</td>
</tr>
</tbody>
</table>

**Policy Statement**

Comprehensive genetic testing for individuals with signs or symptoms of dilated cardiomyopathy which is considered idiopathic after a negative workup for secondary causes may be considered medically necessary.

Targeted genetic testing for asymptomatic individuals with a first-degree relative who has dilated cardiomyopathy and a known familial variant may be considered medically necessary.

Genetic testing for dilated cardiomyopathy is considered investigational in all other situations.

**Policy Guidelines**

**Standard Workup for Patients with Signs or Symptoms of Dilated Cardiomyopathy**

The standard workup for patients with signs or symptoms of dilated cardiomyopathy includes a 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.

**Genetics Nomenclature Update**

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in D and serves as an international standard in D diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s 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 (ACMG) and the Association for Molecular Pathology (AMP) 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,” “variant of uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

| Table PG1. Nomenclature to Report on Variants Found in DNA |
|---------------|-----------------------------|-----------------------------|
| Previous       | Updated                     | Definition                  |
| Mutation       | Disease-associated variant  | Disease-associated change in the DNA sequence |
| Variants       | Change in the DNA sequence |                            |
| Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

| Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification |
|-----------------------------|-----------------------------|
| Variant Classification | Definition                  |
| Pathogenic                 | Disease-causing change in the DNA sequence |
| Likely pathogenic          | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign              | Likely benign change in the DNA sequence |
| Benign                     | Benign change in the DNA sequence |

ACMG: 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:
- 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
- TNNT2 (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: Hereditary 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
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 presentations 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:
- Ischemic coronary artery disease
- Toxins
- Metabolic conditions
- Endocrine disorders
- Inflammatory and infectious diseases
- Infiltrative disorders
- Tachycardia-mediated cardiomyopathy

**Idiopathic Dilated Cardiomyopathy**

When a patient presents with DCM, a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of a 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. Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for secondary causes listed above. This has traditionally been termed 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 a 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 Dilated Cardiomyopathy**

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 lamina A/C, 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 the lamina A/C 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 Idiopathic Dilated Cardiomyopathy

Approximately 30% to 40% of patients with DCM 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 one 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 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 lamin A/C (LM) or desmin (DES) disease-associated variants.

The question addressed in this evidence review is: Does genetic testing improve net 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 are 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.

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 1.

<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 QOL are also important.

The potentially harmful outcomes are those resulting from a false test result. False-positive test results can lead to the 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 the 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.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a 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 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 one type of disease-associated variant 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 2 and explained in more detail below.

Table 2. 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>
</table>
| Haas et al (2015)²²; INHERITANCE | 639 patients with sporadic (51%) or familial (49%) DCM | NGS               | 84 genes     | • Known DCM-causing variants found in 101 (16%) patients
• Likely pathogenic variants found in 147 (23%) patients
• More than 1 DCM-associated variants in 82 (13%) patients |
| Dalin et al (2017)²³ | 176 unrelated patients with idiopathic DCM and 503 healthy reference individuals from European ancestry cohort | NGS               | 41 DCM-related genes | 55 (31%) patients had 1 variant
24 (14%) patients had ≥2 variants |
| Pugh et al (2014)²⁴ | 766 patients with idiopathic DCM                | NGS               | Panels ranging from 5-46 genes | As number of genes tested increased:
• Clinical sensitivity increased from 10% to 37%
• Inconclusive cases increased from 5% to 51% |

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 (Haas et al [2015]), examined a comprehensive set of disease-associated variants and used NGS as the testing method.²² 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&GO²⁵); or benign (identified in the SNP database²⁶ 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.²³ 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 LM, MYH7, or TTN alone, were all associated with early disease onset and reduced transplant-free survival. LM 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%); LM and MYH7 each contributed about 5%.

**Other Sequencing Methods and Clinical Outcomes**

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 was comprised of 96 patients with idiopathic DCM treated at a Canadian clinic. The four genes examined were LM, TNNT2, 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 categorized as clinically significant variants which lead to deletions or truncations, altering proteins which would result in a high probability of causing disease. Four were judged to be variants of uncertain significance (VUS), with the remainder considered benign.

Van der Linde et al (2017) published a retrospective analysis of 80 individuals (15 probands, 65 family members) in the Netherlands who had a variant in the MYH7 gene identified through whole-exome sequencing. 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 MYH7, acknowledging the sample size and length of follow-up were not optimal and could not account for other potential genetic factors.

Myers et al (2018) evaluated the presence of Bcl2-associated anthanogene 3 (BAG3) variants in African Americans with dilated cardiomyopathy and the association of the variants on event-free survival. Genetic testing for BAG3 variants was performed on African American patients from three independent trials (African American Heart Failure Trial, Intervention in Myocarditis and Acute Cardiomyopathy Trial-2, and Genetic Risk Assessment of Cardiac Events study). Among 402 patients with idiopathic DCM, 4 BAG3 variants were detected in 42 (10%) patients. In a population of 359 patients of European ancestry with idiopathic DCM, the prevalence of BAG3 variants was zero. Among the 402 patients with idiopathic DCM, those with BAG3 variants experienced significantly lower event-free survival compared with patients that did not have BAG3 variants (p=0.02).

Verdonschot et al (2018) compared long term outcomes among DCM patients with (n=38) and without (n=265) truncating titin variants (TTNtv). Patients were followed for a median of 45 months (interquartile range 20 to 77 months). Outcomes of interest included cardiac death, heart transplantation, life-threatening ventricular arrhythmias, and unscheduled heart failure hospitalizations. None of the outcomes was significantly different among patients with and without TTNtv except for life-threatening ventricular arrhythmias. Patients with TTNtv experienced significantly more life-threatening ventricular arrhythmias compared with patients without TTNtv (hazard ratio: 2.8; 95% confidence interval: 1.2 to 6.3). Combining the 4 outcomes into a composite endpoint was not statistically significant, possibly due to the small number of patients with TTNtv (hazard ratio: 1.5; 95% confidence interval: 0.7 to 3.1).
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. Thirty-one unique variants were identified in 36 (11.5%) probands. The six genes evaluated (and the frequencies of disease-associated variants identified) were: MYH7 (4.2%), TNNT2 (2.9%), SCN5A (2.6%), TCAP (1.0%), LDB3 (1.0%), and CSRP3 (0.3%). However, only 11 of the 31 probands had variants judged to be probably pathogenic. The remainder were judged to be possible (n=21) or unlikely (n=4) pathogenic.

Millat et al (2011) examined a cohort of 105 unrelated patients with DCM. Sixty-four individuals had familial DCM, and 41 had sporadic DCM. All coding exons and intronic junctions of the MYH7, LM, TNNT2, TNNI3, and 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. Ten genes (MYH7, TNNT2, TNNI3, TPM1, MYBPC3, ACTC, LM, PLN, TAZ, 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 MYH7 (6.6%), LM (5.3%), and TNNT2 (3.7%). VUS were identified in an additional 10.6% (28/264) of individuals.

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 SCN5A gene; also included were 26 healthy individuals. Of the 10 missense variants found, 3 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 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 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 PLN R14del variant carriers, 21% of patients met diagnostic criteria for DCM. In another 2014 retrospective cohort of 41 symptomatic and asymptomatic LM variant carriers, 32% were diagnosed with DCM.

Section Summary: Clinically Valid
Evidence consists of studies in which patients with DCM were tested for specific genes as well as for panels of genes (the panels ranged from 5 to 84 genes). Detection of known and likely DCM-causing variants ranged from 10% to 40%. Additional studies assessed clinical outcomes of patients with DCM and at least one known variant compared with patients with DCM and no known variants. The studies reported that patients with DCM and known variants experienced lower event-free survival, earlier onset of symptoms, lower transplant-free survival, and more life-threatening arrhythmias compared with patients with DCM and no known variants.

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**
There are no randomized controlled trials assessing clinical utility. Below are discussions of two prospective observational studies.

In an observational prospective study, Hasselberg et al (2017) followed 79 individuals with an LM variant who were either symptomatic probands (n=48) or asymptomatic genotype-positive family members (n=31). By the end of 4 years follow-up, 37% of the patients were pacemaker dependent due to third-degree atrioventricular blockage. During an average of 8 years of follow-up, 15 of the 79 probands received heart transplantations. Asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) of cardiac penetrance during an average of 4 years of follow-up. Given the combined likelihood of morbidity and mortality, the requirement for heart transplantation, 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 LM variant be screened due to increased risk.

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 a mean follow-up of 2.2 years, patients with stable or advanced heart disease who had at least one variant showed greater response to -blocker treatment than patients who had no variant (genotype - 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**
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. A prospective observational study has reported that patients with DCM and known variants experienced high rates of morbidity and mortality during four to eight years of follow-up. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management which improve net health outcomes. Changes in management may include earlier implantation of cardiac defibrillators or increased surveillance to detect worsening of symptoms, as well as cascade genetic testing of asymptomatic family members.
Genetic 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 net 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 3. 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, 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%. Brodt et al (2013) conducted a study of 64 (62%) family members identified as carrying the LMNA variant. Fifty-one (79%) of the patients 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 seven years.

Gene identification technologies have increased the number of DCM-associated novel variants but the prevalence and clinical significance remain indeterminate (see Table 4).

Table 4. 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 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 condition was not observed</td>
</tr>
<tr>
<td>Yuan et al (2017)48</td>
<td>Proband and 4 family members with DCM and/or arrhythmia</td>
<td>WES</td>
<td>KCNJ12</td>
<td>Of 12 shared variants identified, the KCNJ12 variant (p.Glu334del) did 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 MYH7) were assessed as potentially damaging or disease-causing; a third 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>BAG3</td>
<td>• 4 other members were described but not tested</td>
</tr>
</tbody>
</table>
2.04.114  Genetic Testing for Idiopathic Dilated Cardiomyopathy
Page 13 of 21

<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>Liu et al (2017)</td>
<td>Family 1: proband and 5 family members with DCM Family 2: asymptomatic proband and 4 family members with DCM</td>
<td>WES</td>
<td>TTN</td>
<td>• Tested individuals showed BAG3 variant (Chr10:121435979-delC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Family 1: Nonsense variant (c.12325C&gt;T/p.R4109X) assessed as disease-causing and -damaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Family 2: Missense variant (c.17755G.C/p.G5919R) absent in control 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. However, several family studies have reported the prevalence of DCM in asymptomatic family members of patients with idiopathic DCM ranging from 20% to 35%.

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.52 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.52 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 they are not at-risk for DCM when they still may have another undiscovered variant.

In the observational prospective study by Hasselberg et al (2017) described above, 31 of the 79 individuals were asymptomatic family members with an LM variant.52 The asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) of cardiac penetrance during an average of 4 years of follow-up. Ten (31%) experienced atrioventricular blockage, 12 experienced ventricular tachycardia, and 7 experienced atrial fibrillations during follow-up. Given the combined likelihood of morbidity and mortality, and the considerable frequency of other cardiac events observed during follow-up in the initially asymptomatic group, the investigators recommended that relatives of probands with known LM variant be screened.
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). 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.

Section Summary: Clinically Useful
There are no randomized controlled trials identified which establish clinical usefulness of genetic testing for asymptomatic family members of patients with known variants. However, a prospective observational study with four to eight years of follow-up reported the development of cardiac symptoms among patients initially asymptomatic who had DCM-related variants. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management which improve net health outcomes. Changes in management may include periodic clinical and cardiovascular evaluations to detect the earliest signs of disease, as well as genetic counseling.

Summary of Evidence
For individuals who have signs and/or symptoms of DCM who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. The relevant outcomes are overall survival, test validity, symptoms, change in disease status, functional outcomes, QOL, and treatment-related morbidity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 40%. Additional studies assessed clinical outcomes of patients with DCM and at least one known variant compared with patients with DCM and no known variants. The studies reported that patients with DCM and known variants experienced lower event-free survival, earlier onset of symptoms, lower transplant-free survival, and more life-threatening arrhythmias compared with patients with DCM and no known variants. A prospective observational study has reported that patients with DCM and known variants experienced high rates of morbidity and mortality during four to eight years of follow-up. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management which improve net health outcomes. Changes in management may include earlier implantation of cardiac defibrillators or increased surveillance to detect worsening of symptoms, as well as cascade genetic testing of asymptomatic family members. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 clinical value and a prospective observational study reporting clinical utility. The relevant outcomes are test validity, symptoms, morbid events, functional outcomes, QOL, 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. A prospective observational study with four to eight years of follow-up reported the development of cardiac symptoms among patients initially asymptomatic who had DCM-related variants. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management which improve net health outcomes. Changes in management may include periodic clinical and cardiovascular evaluations to detect the earliest signs of disease, as well as genetic counseling. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Supplemental Information
Practice Guidelines and Position Statements

American Heart Association

In a scientific statement from the AHA (2016) regarding diagnostic and treatment strategies for specific dilated cardiomyopathy (DCM), the AHA states that “A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies.”

Table 5 summarizes the AHA recommendations regarding genetic testing for patients with DCM.

Table 5. Genetic Testing Recommendations for DCM by the American Heart Association

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.</td>
<td>B</td>
</tr>
<tr>
<td>In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling.</td>
<td>B</td>
</tr>
<tr>
<td>Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to facilitate cascade screening within the family, and to help with family planning.</td>
<td>A</td>
</tr>
<tr>
<td>Recommendations for Pediatric DCM</td>
<td></td>
</tr>
<tr>
<td>Compenduous or targeted DCM genetic testing (LMNA and SCN5A) is recommended for patients with DCM and significant cardiac conduction disease (i.e., first-, second-, or third-degree heart block) or a family history of premature unexpected sudden death.</td>
<td>A</td>
</tr>
<tr>
<td>Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.</td>
<td>B</td>
</tr>
<tr>
<td>Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, facilitate cascade screening within the family, and help with family planning.</td>
<td>A</td>
</tr>
<tr>
<td>In pediatric patients with DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered.</td>
<td>C</td>
</tr>
</tbody>
</table>

LOE: level of evidence

American College of Medical Genetics and Genomics

The ACMG (2018) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for all types of 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.

The ACMG also provided information on specific variants, noting that TTNtv represents the most common genetic variant found in DCM (10% to 20% of cases), with LMNA being the second most common variant identified (diagnostic yield of 5.5%).

When a cardiovascular phenotype has been identified, the ACMG recommends family-based genetic evaluations and surveillance screening.

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and European Heart Rhythm Association (2011) issued joint guidelines on genetic testing for cardiac channelopathies and cardiomyopathies. These guidelines included the following recommendations on genetic testing for DCM (see Table 6).
Table 6. Genetic Testing Recommendations for DCM by the Heart Rhythm Society and European Heart Rhythm Association

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Comprehensive or targeted (LM 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.&quot;</td>
<td>I</td>
</tr>
<tr>
<td>&quot;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.&quot;</td>
<td>I</td>
</tr>
<tr>
<td>&quot;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.&quot;</td>
<td>Ila</td>
</tr>
</tbody>
</table>

COR: class of recommendation (I: recommended; Ila: can be useful); 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 (LM or Desmin [DES]).

Heart Failure Society of America
The Heart Failure Society of America (2018) published practice guidelines 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
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 ongoing and unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</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>NC02148926</td>
<td>Clinical and Genetic Examinations of Dilated Cardiomyopathy</td>
<td>4554</td>
<td>Jun 2018 (ongoing)</td>
</tr>
<tr>
<td>NC03572569</td>
<td>Risk Stratification in Children and Adolescents with Primary Cardiomyopathy</td>
<td>200</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NC03037632</td>
<td>Precision Medicine for Dilated Cardiomyopathy in European and African Ancestry</td>
<td>6500</td>
<td>Jun 2021</td>
</tr>
<tr>
<td>NC01736566</td>
<td>The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine</td>
<td>2213</td>
<td>Aug 2022 (ongoing)</td>
</tr>
<tr>
<td>NC01857856</td>
<td>PHospholamban RElated Cardiomyopathy Study - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)</td>
<td>182</td>
<td>Jul 2021</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC02057341</td>
<td>A Study of ARRY-371797 in Patients With LM-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.
2.04.114 Genetic Testing for Idiopathic Dilated Cardiomyopathy

- Reason for performing test
- Signs/symptoms/test results related to reason for genetic testing
- Physician’s order for genetic test(s)
- Name and description of genetic test(s)
- Report(s) of prior work-up for dilated cardiomyopathy
- Family history of dilated cardiomyopathy including:
  - Family relationship (if applicable)
  - Genetic mutation analysis results in the relative (if applicable)

Post Service
- Results/reports of tests performed

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.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is 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</td>
</tr>
<tr>
<td>CPT®</td>
<td>81405</td>
<td>Molecular pathology procedure, Level 6</td>
</tr>
<tr>
<td>CPT®</td>
<td>81406</td>
<td>Molecular pathology procedure, Level 7</td>
</tr>
<tr>
<td>CPT®</td>
<td>81407</td>
<td>Molecular pathology procedure, Level 8</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 sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Procedure</td>
<td>None</td>
<td>None</td>
</tr>
</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>
2.04.114  Genetic Testing for Idiopathic Dilated Cardiomyopathy
Page 21 of 21

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/2019</td>
<td>Policy title change from Genetic Testing for Dilated Cardiomyopathy</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td></td>
<td>Policy revision with position change</td>
<td></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.