2.04.114	Genetic Testing for Idiopathic Dilated Cardiomyopathy		
Original Policy Date:	April 30, 2015	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 26

Policy Statement

I. 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**.

II. 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**.

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 (DCM) includes a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. An 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 nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

Previous	Updated	Definition
	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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

See the Codes table for details.

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.

Summary of Evidence

For individuals who have signs and/or symptoms of dilated cardiomyopathy (DCM) who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. Relevant outcomes are overall survival, test validity, symptoms, change in disease status, functional outcomes, quality of life, 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 1 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 4 to 8 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 an 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 retrospective studies and case series reporting clinical value and a prospective observational study reporting clinical utility. Relevant outcomes are test 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. A prospective observational study with 4 to 8 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 an improvement in the net health outcome.

Additional Information

Not applicable.

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 member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services 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 law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 496

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview

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 (CLIA). Laboratories that offer laboratory-developed tests

must be licensed by the CLIA 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. Dilated cardiomyopathy 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,]

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. An extensive workup including cardiac magnetic resonance imaging (MRI), exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM.[3,] Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for the secondary causes listed above.[4,] This has traditionally been termed idiopathic dilated cardiomyopathy (IDC).

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

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.[5,] Expanded numbers of genotyped individuals facilitate genotype-phenotype correlations and studies of natural disease history.[6,] Recognition of high-risk variant carriers is important as these individuals would be expected to have the most to gain from pre-emptive interventions.

In general, genotype-phenotype correlations in the inherited cardiomyopathies 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 lamin A/C (LM), *SCN5A*, and desmin genes.[1,] Kayvanpour et al (2017) performed a meta-analysis of genotype-phenotype associations in DCM.[7,] The analysis included 48 studies (N=8097) and found a higher prevalence of sudden cardiac death, cardiac transplantation, and ventricular arrhythmias in the LM and phospholamban (PLN) disease-associated variant carriers and increasing penetrance with age of DCM phenotype in subjects with titin (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.[2,] 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.

Diagnosis of Dilated Cardiomyopathy

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[4,]:

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

Treatment of Dilated Cardiomyopathy

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 Testing for Dilated Cardiomyopathy

Approximately 30% to 40% of patients with DCM referred for genetic testing will have a disease-associated variant identified.[1,] 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 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.[5,] 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.[1,] 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 Individuals with Signs and/or Symptoms of Dilated Cardiomyopathy

Clinical Context and Test Purpose

The purpose of genetic testing in individuals 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 individuals with DCM are generally based on cardiac phenotype, although the prophylactic placement of a pacemaker and/or implantable cardioverter-defibrillator is sometimes considered in individuals with DCM and lamin A/C (LM) or desmin disease-associated variants.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals 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.[8,]

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.

Comparators

The comparator of interest is standard clinical care without genetic testing such that decisions regarding medical therapy in symptomatic individuals with DCM are being made based on cardiac phenotype.

Outcomes

Specific outcomes are listed in Table 1.

Table 1. Outcomes of Interest for Individuals with Symptomatic Dilated Cardiomyopathy

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

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 the initiation of unnecessary treatment and adverse events from that treatment. In this case, unnecessary treatment would include placement of an implantable cardioverter-defibrillator.

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.[9,10] Therefore, 2-year survival and changes in other outcomes over the same period should be considered meaningful in this review.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for DCM, methodologically credible studies were selected using the following eligibility criteria:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.
- Included a validation cohort separate from the development cohort.

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).

Review of Evidence

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 variant in probands with DCM or family members of the proband.[11-20] 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 (VUS).[21,22,20,23] Hofmeyer et al (2023) specifically evaluated the association of rare variant genetics and advanced DCM using data from the US multisite DCM Precision Medicine Study.[24] The DCM Precision Medicine Study aimed to test the hypothesis that DCM has a substantial genetic basis and to evaluate the effectiveness of a family communication intervention in improving the uptake of family member clinical screening. Hofmeyer et al classified rare variants in 36 DCM genes as pathogenic or likely pathogenic or VUS.

Next-Generation Sequencing

The studies evaluating multiple genes using NGS or whole-exome sequencing are summarized in Table 2 and are explained in more detail below.

Table 2. Studies Evaluating the Clinical Validity of Genetic Testing for Dilated Cardiomyopathy Using Next-Generation Sequencing

Study	Population	Sequencing Method	Genes Tested	Results
Hofmeyer et al (2023)[24]	1198 patients with advanced DCM enrolled in the US multisite DCM Precision Medicine Study	Exome sequencing	36 genes	• The percentage of patients with pathogenic or likely pathogenic rare variants was 26.2%, 15.9%, and 15.0% for those who had received a left ventricular assist device or heart transplant, implantable cardioverter defibrillator only, or neither, respectively. • Patients with DCM who had received a left

Study	Population	Sequencing Method	Genes Tested	Results
				ventricular assist device or a heart transplant were more likely to have pathogenic or likely pathogenic DCM-related rare variants as compared to those who did not have a left ventricular assist device, a heart transplant, or an implantable cardioverter defibrillator (OR, 2.3; 95% CI, 1.5 to 3.6).
van der Meulen (2022)[23,]	144 children with DCM in the Netherlands (107 [74%] underwent genetic testing)	NGS (63%); Sanger sequencing (15%); exome sequencing (31%)	28 to 70 genes	• 36% (n=38) of patients carried a likely pathogenic/pathogenic variant • 37% (n=40) of patients carried 1 or more variant of unknown significance • 27% (n=29) of patients had no variants • *MYH7* was the largest contributor of pathogenic variants (21%); *TTN* and *TPM1* were the second highest (8%)
Dalin et al (2017)[25,]	176 unrelated patients with idiopathic DCM and 503 healthy reference individuals from a European ancestry cohort	NGS	41 DCM-related genes	• 55 (31%) patients had 1 variant • 24 (14%) patients had ≥2 variants
Haas et al (2015)[26,]; 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 variant in 82 (13%) patients
Pugh et al (2014)[27,]	766 patients with idiopathic DCM	NGS	Panels ranging from 5 to 46 genes	As number of genes tested increased: • Clinical sensitivity increased from 10% to 37% • Inconclusive cases increased from 5% to 51%

CI: confidence interval; DCM: dilated cardiomyopathy; INHERITANCE: INtegrated HEart Research In TrANslational genetics of dilated Cardiomyopathies in Europe; NGS: next-generation sequencing; OR: odds ratio.

The largest study to date, the Integrated Heart Research in Translational Genetics of Dilated Cardiomyopathies in Europe (INHERITANCE) project, examined a comprehensive set of disease-associated variants and used NGS as the testing method.[26,] 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. Next-generation sequencing 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 an online calculator, SNPs&GO[28,]); or benign (identified in the SNP database[8,] 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.

van der Meulen (2022) performed a genetic evaluation of 107 Dutch children with DCM.[23,] Sixteen patients (15%) underwent Sanger sequencing of one or more genes and 67 (63%) patients had a targeted gene panel using NGS (including those who also had undergone Sanger sequencing and/or exome sequencing). Thirty-three patients (31%) had exome sequencing with analysis of an expanded gene panel related to cardiomyopathy, and 1 patient had their genome sequenced with comprehensive analysis of all known genes. Three patients had their DNA analyzed with other techniques. Results showed that 38 (36%) patients carried a likely pathogenic/pathogenic variant, including 11 who had 1 or more additional VUSs. Forty patients (37%) had only 1 or more VUS, whereas 29 (27%) patients had no variant. Likely pathogenic/pathogenic variants were found in 21 different genes, with *MYH7*being the largest contributor of pathogenic variants (8 likely pathogenic/ pathogenic variants [21%]). The second highest contributors were *TTN* and *TPM1*, each accounting for 8% of positive test results.

Dalin et al (2017) used NGS to sequence the coding regions of 41 DCM-associated genes in 176 unrelated patients with idiopathic DCM, which were compared with 503 healthy reference individuals in the European ancestry cohort of the 1000 Genomes project.[25,] 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. Lamin A/C 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=.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% in DCM patients and 37% in 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 idiopathic DCM patients tested over 5 years at a single molecular diagnostics laboratory.[27,] 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. Titin 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.[29,] The population was comprised of 96 patients with idiopathic DCM treated at a Canadian clinic. The 4 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, 7 of which were novel. Two variants were categorized as clinically significant variants, which lead to deletions or truncations, altering proteins that would result in a high probability of causing disease. Four were judged to be 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.[30,] 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 DCM and the association of the variants on event-free survival.[31,] Genetic testing for *BAG3* variants was performed on African American patients from 3 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=.02).

Verdonschot et al (2018) compared long-term outcomes among DCM patients with (n=38) and without (n=265) truncating titin variants (TTNtv).[32,] 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 [HR] , 2.8; 95% confidence interval [CI] , 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 (HR] , 1.5; 95% CI] , 0.7 to 3.1).

Ebert et al (2020) evaluated the frequency of (likely) pathogenic variants among 98 patients with DCM referred for ventricular tachycardia ablation.[33,] All patients underwent electroanatomical mapping and testing of ≥55 cardiomyopathy-related genes. Likely pathogenic/pathogenic variant-positive patients were compared with likely pathogenic/pathogenic variant negative patients and followed for ventricular tachycardia recurrence. In 37 (38%) patients, likely pathogenic/pathogenic variants were identified, most frequently *LMNA* (30%), *TTN* (16%), *SCN5A* (8%), *RBM20* (5%), and *DSP* (5%). Likely pathogenic/pathogenic variant-positive carriers had a lower left ventricular ejection fraction as compared to likely pathogenic/pathogenic variant-negative carriers (35% vs. 42%; p=.005). After a median follow-up of 2.4 years, 63 (64%) patients had ventricular tachycardia recurrence (81% pathogenic variant-positive vs. 54% pathogenic variant-negative; p=.007) and 28 (29%) patients died (51% pathogenic variant-positive vs. 15% pathogenic variant-negative; p<.001). 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.

Millat et al (2011) examined a cohort of 105 unrelated patients with DCM.[34,] 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 9 were previously described variants.

Lakdawala et al (2012) studied 264 unrelated adults and children with DCM, approximately half of whom had familial disease.[35,] 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) of individuals with DCM. Genes with the most frequent pathogenic variants were *MYH7* (6.6%), *LM* (5.3%), and *TNNT2* (3.7%). A VUS was 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 the *SCN5A* gene; also included were 26 healthy individuals.[36,] 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* 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.[37,] In another 2014 retrospective cohort of 41 symptomatic and asymptomatic *LM* variant carriers, 32% were diagnosed with DCM.[38,]

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, more effective therapy, or avoid unnecessary therapy or 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 (RCTs).

Chain of Evidence

There are no RCTs assessing clinical utility. Below are discussions of select 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).[39,] By the end of 4 years of 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) 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.[40,] 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 1 variant showed greater response to ß-blocker treatment than patients who had no variant (genotype ß-blocker interaction p-values ≤.05 for several hemodynamic parameters). Wasielewski et al (2014) reported on a descriptive study investigating whether familial DCM may predispose to anthracycline-associated cardiomyopathy.[41,] 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: Patients with Signs and/or Symptoms of Dilated Cardiomyopathy
The 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 1 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. 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 4 to 8 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 individuals 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 individuals.

The following PICO was used to select literature to inform this review.

Populations
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. Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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 3.

Table 3. Outcomes of Interest for Asymptomatic Individuals With a Relative With Dilated Cardiomyopathy

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

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

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 an 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.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for DCM, methodologically credible studies were selected using the following eligibility criteria:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.
- Included a validation cohort separate from the development cohort.

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).

Review of Evidence
Several studies have described the prevalence of DCM in family members of patients diagnosed with idiopathic DCM, with estimates ranging from 11% to 44%.[42,43,44,45,] Brodt et al (2013) conducted a study of 64 (62%) family members identified as carrying the *LMNA* variant.[46,]Fifty-one (79%) of the patients

had electrocardiographic abnormalities at initial screening (mean age of onset, 41 years; range, 18 to 76 years). Twenty-six (25%) had ventricular dysfunction (mean age of onset, 48 years; range, 28 to 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.

Huggins et al (2022) published the DCM Precision Medicine Study, which included a cross-sectional sub-study of families at 25 US clinical sites with advanced heart failure programs that investigated the prevalence of familial disease amongst patients with idiopathic DCM as well as the lifetime risk of DCM in first-degree relatives.[47,] The study cohort included 1220 patients with DCM probands and 1693 first-degree relatives. Overall, 11.6% of first-degree relatives had DCM probands. Crude prevalences of familial DCM were 10.9% among non-Hispanic Black and 12.0% among non-Hispanic White probands. In a model-based estimate, the prevalence of familial DCM at a typical US advanced heart failure program if all living first-degree relatives were screened was 29.7% (95% CI, 23.5% to 36.0%), and the estimated risk by age 80 years in first-degree relatives was 19%. Furthermore, the prevalence of familial DCM was higher in Black probands than in White probands (difference, 11.3%; 95% CI, 1.9% to 20.8%) but did not significantly differ between Hispanic probands and non-Hispanic probands (difference, -1.4%; 95% CI, -15.9% to 13.1%).

Vissing et al (2022) published a retrospective, cohort study of 211 families (n=563) screened and followed from 2006 to 2020 at a regional assembly of clinics for inherited cardiomyopathies in Denmark.[48,] At baseline, 124 relatives (22%) were diagnosed with familial DCM. During a median follow-up of 5.0 years, an additional 45 individuals developed DCM, increasing the overall yield to 34%.

Stava et al (2022) retrospectively evaluated data from 2003 to 2020 from the laboratory information management system at Unit for Cardiac and Cardiovascular Genetics at Oslo University hospital in Norway.[49,] Data from 4408 cardiomyopathy probands identified a 14.1% hit-rate of genetic testing for DCM. Furthermore, 44.1% of relatives were positive for a DCM variant previously found in their family. The most common DCM variant in probands and relatives combined was the c.40_42del variant in *PLN*, accounting for 19% of all DCM variants.

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

Table 4. Familial Studies and Case Reports of Dilated Cardiomyopathy-Associated Novel Variants

Study	Population	Sequencing Type	Gene Tested	Results
Huggins et al (2022)[47,]	Patients with DCM (n=1220 probands) and their first-degree relatives (n=1693)	Exome sequencing	NR	• The crude prevalence of familial DCM among probands was 11.6% • A model-based estimate of DCM risk by age 80 years in first-degree relatives was 19% • A model-based estimate of the prevalence of familial DCM among probands if all living first-degree relatives were screened was 29.7% (95% CI, 23.5% to 36.0%)
Stava et al (2022)[49,]	Patients with DCM (n=1541 probands) and their relatives (n=1045)	Sanger sequencing (until 2015); Sanger sequencing and/or	Multiple	• Data from 4408 cardiomyopathy probands identified a 14.1% hit-rate for DCM • 44.1% of the relatives were positive for a variant previously found in their family

Study	Population	Sequencing Type	Gene Tested	Results
		NGS (since 2015)		• The most common DCM variant in probands and relatives combined was the c.40_42del variant in *PLN*, accounting for 19% of all DCM variants
Vissing et al (2022)[48,]	211 families with inherited cardiomyopathies (n=563)	NR	Multiple	• At baseline, 124 individuals (22%) were diagnosed with familial DCM • During a median follow-up of 5.0 years, an additional 45 individuals developed DCM, increasing the overall yield to 34%
Fernlund et al (2017)[50,]	11-mo proband with DCM and 6 family members	NGS	*TNNT2*, *BAG3*	• 4 individuals had *TNNT2*-variant; 2 had *TNNT2*and *BAG3*variants • Onset and severity of disease varied
Asadi et al (2017)[51,]	6 members of a family with a history of CHF	NGS	*δ-Sg*	2 individuals had a heterozygous variant (p.R97Q) in *δ-Sg* gene; the variant was not found in 100 controls
Bodian et al (2017)[52,]	Infant proband with intractable diarrhea and DCM	WGS	*EPCAM*	The *EPCAM*-variant (c.556-14A>G) suggests intestinal tufting, but this condition was not observed
Yuan et al (2017)[53,]	Proband and 4 family members with DCM and/or arrhythmia	WES	*KCNJ12*	Of 12 shared variants identified, the *KCNJ12*variant (p.Glu334del) did not appear in European or African registries
Petropoulou et al (2017)[54,]	Proband and 1 family member with atypical DCM	WES	*TNNT2*, *MYH7*	Variants found (c.247A>C; p.Asn83His in *TNNT2*; c.2863G>A; p.Asp955Asn in *MYH7*) were assessed as potentially damaging or disease-causing; a third variant in *PRDM16*was inconclusively associated with cardiomyopathy
Rafiq et al (2017) [55,]	3 members of a family with history of DCM	WES	*BAG3*	• 4 other members were described but not tested • Tested individuals showed *BAG3*variant (Chr10:121435979-delC)
Liu et al (2017)[56,]	Family 1: proband and 5 family members with DCM Family 2: asymptomatic proband and 4 family members with DCM	WES	*TTN*	• Family 1: Nonsense variant (c.12325C>T/p.R4109X) assessed as disease-causing and -damaging • Family 2: Missense variant (c.17755G.C/p.G5919R) absent in control cohort

CHF: congestive heart failure; CI: confidence interval; DCM: dilated cardiomyopathy; NGS: next-generation sequencing; NR: not reported; WES: whole-exome sequencing; WGS: whole-genome sequencing.

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, more effective therapy, or avoid unnecessary therapy or testing.

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.

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.[57,] 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.[57,] 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 *LMN* variant.[39,] The asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) cardiac penetrance during an average of 4 years of follow-up. Ten (31%) experienced atrioventricular blockage, 12 experienced ventricular tachycardia, and 7 experienced atrial fibrillation 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 *LMN* 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 1 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: Testing Asymptomatic Individuals to Determine Future Risk

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 retrospective studies and case series and reports describing the prevalence of the most common genetic variants or the yield of targeted testing. Several family studies have reported the prevalence of DCM in asymptomatic family members of patients with idiopathic DCM ranging from 11% to 44%. In a family-based, cross-sectional study of patients with DCM and first-degree relatives at 25 US advanced heart failure programs, the crude prevalence of familial DCM was 11.6%; furthermore, a model-based estimate suggests a prevalence of familial DCM of 29.7% if all living first-degree relatives were screened. There are no RCTs identified that establish the clinical usefulness of genetic testing for asymptomatic

family members of patients with known variants. However, a prospective observational study with 4 to 8 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association

In 2016, the American Heart Association (AHA) released a scientific statement regarding diagnostic and treatment strategies for specific dilated cardiomyopathy (DCM), the AHA stated: "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."[58,] Table 5 summarizes the AHA recommendations regarding genetic testing for patients with DCM.

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

Recommendation	LOE
Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.	B
In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling.	B
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.	A
Recommendations for Pediatric DCM	LOE
Comprehensive 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.	A
Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.	B
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.	A
In pediatric patients with a DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered.	C

DCM: dilated cardiomyopathy; LOE: level of evidence.

American College of Medical Genetics and Genomics

In 2018, the American College of Medical Genetics and Genomics (ACMG) published clinical practice recommendations for the genetic evaluation of cardiomyopathy.[59,] The following recommendations were made for all types of cardiomyopathy:

- Genetic testing is recommended for the most clearly affected family member.
- Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.

- 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

In 2011, the Heart Rhythm Society and European Heart Rhythm Association issued a consensus statement on genetic testing for cardiac channelopathies and cardiomyopathies.[60,]The statement included the following recommendations on genetic testing for DCM that were reaffirmed in 2018 (Table 6).

Table 6. Genetic Testing Recommendations for Dilated Cardiomyopathy by the Heart Rhythm Society and European Heart Rhythm Association

Recommendation	COR
"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."	I
"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."	I
"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."	IIa

COR: class of recommendation (I: recommended; IIa: can be useful); DCM: dilated cardiomyopathy.

The 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]).[60,]

Heart Failure Society of America

In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy.[61,] 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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04572893	Open-Label Exploratory Study of Oral MYK-491 in Stable Ambulatory Patients With Primary Dilated Cardiomyopathy Due to Either MYH7 or TTN Variants	24	Jan 2025
NCT01736566	The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine	213	Aug 2022
NCT03860454	The Deep Phenotype of Lamin A/C Cardiomyopathy - A Proof-of-Principle Relax-omic Pipeline	150	Feb 2025
NCT03843255	Defining the Genetics, Biomarkers and Outcomes for Dilated Cardiomyopathy: a Prospective Multicentre Observational Study	2000	Jul 2027
Unpublished			
NCT02148926	Clinical and Genetic Examinations of Dilated Cardiomyopathy	4554	Jun 2018 (unknown)
NCT01857856	PHOspholamban RElated CArdiomyopathy STudy - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)	84	Oct 2021

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

References

1. Hersheberger RE, Morales A. Dilated Cardiomyopathy Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2015.
2. Piran S, Liu P, Morales A, et al. Where genome meets phenome: rationale for integrating genetic and protein biomarkers in the diagnosis and management of dilated cardiomyopathy and heart failure. J Am Coll Cardiol. Jul 24 2012; 60(4): 283-9. PMID 22813604
3. Broch K, Andreassen AK, Hopp E, et al. Results of comprehensive diagnostic work-up in 'idiopathic' dilated cardiomyopathy. Open Heart. 2015; 2(1): e000271. PMID 26468400
4. Hershberger RE, Morales A, Siegfried JD. Clinical and genetic issues in dilated cardiomyopathy: a review for genetics professionals. Genet Med. Nov 2010; 12(11): 655-67. PMID 20864896
5. Lakdawala NK, Winterfield JR, Funke BH. Dilated cardiomyopathy. Circ Arrhythm Electrophysiol. Feb 2013; 6(1): 228-37. PMID 23022708
6. Fatkin D, Huttner IG, Kovacic JC, et al. Precision Medicine in the Management of Dilated Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. Dec 10 2019; 74(23): 2921-2938. PMID 31806137
7. Kayvanpour E, Sedaghat-Hamedani F, Amr A, et al. Genotype-phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. Clin Res Cardiol. Feb 2017; 106(2): 127-139. PMID 27576561
8. National Center for Biotechnology Infomation. GTR: Genetic Testing Registry. n.d.; https://www.ncbi.nlm.nih.gov/gtr/. Accessed December 12, 2024.
9. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. May 20 2004; 350(21): 2151-8. PMID 15152060
10. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. Jan 20 2005; 352(3): 225-37. PMID 15659722
11. Brodsky GL, Muntoni F, Miocic S, et al. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. Circulation. Feb 08 2000; 101(5): 473-6. PMID 10662742
12. MacLeod HM, Culley MR, Huber JM, et al. Lamin A/C truncation in dilated cardiomyopathy with conduction disease. BMC Med Genet. Jul 10 2003; 4: 4. PMID 12854972

13. Olson TM, Michels VV, Thibodeau SN, et al. Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. Science. May 01 1998; 280(5364): 750-2. PMID 9563954
14. Sylvius N, Duboscq-Bidot L, Bouchier C, et al. Mutational analysis of the beta- and delta-sarcoglycan genes in a large number of patients with familial and sporadic dilated cardiomyopathy. Am J Med Genet A. Jul 01 2003; 120A(1): 8-12. PMID 12794684
15. Taylor MR, Slavov D, Ku L, et al. Prevalence of desmin mutations in dilated cardiomyopathy. Circulation. Mar 13 2007; 115(10): 1244-51. PMID 17325244
16. Villard E, Duboscq-Bidot L, Charron P, et al. Mutation screening in dilated cardiomyopathy: prominent role of the beta myosin heavy chain gene. Eur Heart J. Apr 2005; 26(8): 794-803. PMID 15769782
17. Dhandapany PS, Razzaque MA, Muthusami U, et al. RAF1 mutations in childhood-onset dilated cardiomyopathy. Nat Genet. Jun 2014; 46(6): 635-639. PMID 24777450
18. McNair WP, Sinagra G, Taylor MR, et al. SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol. May 24 2011; 57(21): 2160-8. PMID 21596231
19. van Rijsingen IA, Nannenberg EA, Arbustini E, et al. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. Eur J Heart Fail. Apr 2013; 15(4): 376-84. PMID 23183350
20. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. Feb 16 2012; 366(7): 619-28. PMID 22335739
21. Theis JL, Sharpe KM, Matsumoto ME, et al. Homozygosity mapping and exome sequencing reveal GATAD1 mutation in autosomal recessive dilated cardiomyopathy. Circ Cardiovasc Genet. Dec 2011; 4(6): 585-94. PMID 21965549
22. Norton N, Li D, Rieder MJ, et al. Genome-wide studies of copy number variation and exome sequencing identify rare variants in BAG3 as a cause of dilated cardiomyopathy. Am J Hum Genet. Mar 11 2011; 88(3): 273-82. PMID 21353195
23. van der Meulen MH, Herkert JC, den Boer SL, et al. Genetic Evaluation of A Nation-Wide Dutch Pediatric DCM Cohort: The Use of Genetic Testing in Risk Stratification. Circ Genom Precis Med. Oct 2022; 15(5): e002981. PMID 36178741
24. Hofmeyer M, Haas GJ, Jordan E, et al. Rare Variant Genetics and Dilated Cardiomyopathy Severity: The DCM Precision Medicine Study. Circulation. Sep 12 2023; 148(11): 872-881. PMID 37641966
25. Dalin MG, Engström PG, Ivarsson EG, et al. Massive parallel sequencing questions the pathogenic role of missense variants in dilated cardiomyopathy. Int J Cardiol. Feb 01 2017; 228: 742-748. PMID 27886618
26. Haas J, Frese KS, Peil B, et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J. May 07 2015; 36(18): 1123-35a. PMID 25163546
27. Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. Genet Med. Aug 2014; 16(8): 601-8. PMID 24503780
28. University of Bologna. ws-SNPs&GO. n.d.; http://snps.biofold.org/snps-and-go//index.html. Accessed December 12, 2024.
29. Hirtle-Lewis M, Desbiens K, Ruel I, et al. The genetics of dilated cardiomyopathy: a prioritized candidate gene study of LMNA, TNNT2, TCAP, and PLN. Clin Cardiol. Oct 2013; 36(10): 628-33. PMID 24037902
30. van der Linde IHM, Hiemstra YL, Bökenkamp R, et al. A Dutch MYH7 founder mutation, p.(Asn1918Lys), is associated with early onset cardiomyopathy and congenital heart defects. Neth Heart J. Dec 2017; 25(12): 675-681. PMID 28864942
31. Myers VD, Gerhard GS, McNamara DM, et al. Association of Variants in BAG3 With Cardiomyopathy Outcomes in African American Individuals. JAMA Cardiol. Oct 01 2018; 3(10): 929-938. PMID 30140897
32. Verdonschot JAJ, Hazebroek MR, Derks KWJ, et al. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur Heart J. Mar 07 2018; 39(10): 864-873. PMID 29377983

33. Ebert M, Wijnmaalen AP, de Riva M, et al. Prevalence and Prognostic Impact of Pathogenic Variants in Patients With Dilated Cardiomyopathy Referred for Ventricular Tachycardia Ablation. JACC Clin Electrophysiol. Sep 2020; 6(9): 1103-1114. PMID 32972544
34. Millat G, Bouvagnet P, Chevalier P, et al. Clinical and mutational spectrum in a cohort of 105 unrelated patients with dilated cardiomyopathy. Eur J Med Genet. 2011; 54(6): e570-5. PMID 21846512
35. Lakdawala NK, Funke BH, Baxter S, et al. Genetic testing for dilated cardiomyopathy in clinical practice. J Card Fail. Apr 2012; 18(4): 296-303. PMID 22464770
36. Priganc M, Zigová M, Boroňová I, et al. Analysis of SCN5A Gene Variants in East Slovak Patients with Cardiomyopathy. J Clin Lab Anal. Mar 2017; 31(2). PMID 27554632
37. van Rijsingen IA, van der Zwaag PA, Groeneweg JA, et al. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. Circ Cardiovasc Genet. Aug 2014; 7(4): 455-65. PMID 24909667
38. Hasselberg NE, Edvardsen T, Petri H, et al. Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. Europace. Apr 2014; 16(4): 563-71. PMID 24058181
39. Hasselberg NE, Haland TF, Saberniak J, et al. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. Eur Heart J. Mar 07 2018; 39(10): 853-860. PMID 29095976
40. Reddy S, Fung A, Manlhiot C, et al. Adrenergic receptor genotype influences heart failure severity and β-blocker response in children with dilated cardiomyopathy. Pediatr Res. Feb 2015; 77(2): 363-9. PMID 25406899
41. Wasielewski M, van Spaendonck-Zwarts KY, Westerink ND, et al. Potential genetic predisposition for anthracycline-associated cardiomyopathy in families with dilated cardiomyopathy. Open Heart. 2014; 1(1): e000116. PMID 25332820
42. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med. Jan 09 1992; 326(2): 77-82. PMID 1727235
43. Grünig E, Tasman JA, Kücherer H, et al. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol. Jan 1998; 31(1): 186-94. PMID 9426039
44. Baig MK, Goldman JH, Caforio AL, et al. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol. Jan 1998; 31(1): 195-201. PMID 9426040
45. Mahon NG, Murphy RT, MacRae CA, et al. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease. Ann Intern Med. Jul 19 2005; 143(2): 108-15. PMID 16027452
46. Brodt C, Siegfried JD, Hofmeyer M, et al. Temporal relationship of conduction system disease and ventricular dysfunction in LMNA cardiomyopathy. J Card Fail. Apr 2013; 19(4): 233-9. PMID 23582089
47. Huggins GS, Kinnamon DD, Haas GJ, et al. Prevalence and Cumulative Risk of Familial Idiopathic Dilated Cardiomyopathy. JAMA. Feb 01 2022; 327(5): 454-463. PMID 35103767
48. Vissing CR, Espersen K, Mills HL, et al. Family Screening in Dilated Cardiomyopathy: Prevalence, Incidence, and Potential for Limiting Follow-Up. JACC Heart Fail. Nov 2022; 10(11): 792-803. PMID 36328645
49. Stava TT, Leren TP, Bogsrud MP. Molecular genetics in 4408 cardiomyopathy probands and 3008 relatives in Norway: 17 years of genetic testing in a national laboratory. Eur J Prev Cardiol. Oct 18 2022; 29(13): 1789-1799. PMID 35653365
50. Fernlund E, Österberg AW, Kuchinskaya E, et al. Novel Genetic Variants in BAG3 and TNNT2 in a Swedish Family with a History of Dilated Cardiomyopathy and Sudden Cardiac Death. Pediatr Cardiol. Aug 2017; 38(6): 1262-1268. PMID 28669108
51. Asadi M, Foo R, Salehi AR, et al. Mutation in δ-Sg Gene in Familial Dilated Cardiomyopathy. Adv Biomed Res. 2017; 6: 32. PMID 28401079

52. Bodian DL, Vilboux T, Hourigan SK, et al. Genomic analysis of an infant with intractable diarrhea and dilated cardiomyopathy. Cold Spring Harb Mol Case Stud. Nov 2017; 3(6). PMID 28701297
53. Yuan HX, Yan K, Hou DY, et al. Whole exome sequencing identifies a KCNJ12 mutation as a cause of familial dilated cardiomyopathy. Medicine (Baltimore). Aug 2017; 96(33): e7727. PMID 28816949
54. Petropoulou E, Soltani M, Firoozabadi AD, et al. Digenic inheritance of mutations in the cardiac troponin (TNNT2) and cardiac beta myosin heavy chain (MYH7) as the cause of severe dilated cardiomyopathy. Eur J Med Genet. Sep 2017; 60(9): 485-488. PMID 28642161
55. Rafiq MA, Chaudhry A, Care M, et al. Whole exome sequencing identified 1 base pair novel deletion in BCL2-associated athanogene 3 (BAG3) gene associated with severe dilated cardiomyopathy (DCM) requiring heart transplant in multiple family members. Am J Med Genet A. Mar 2017; 173(3): 699-705. PMID 28211974
56. Liu JS, Fan LL, Zhang H, et al. Whole-Exome Sequencing Identifies Two Novel TTN Mutations in Chinese Families with Dilated Cardiomyopathy. Cardiology. 2017; 136(1): 10-14. PMID 27544385
57. Posafalvi A, Herkert JC, Sinke RJ, et al. Clinical utility gene card for: dilated cardiomyopathy (CMD). Eur J Hum Genet. Oct 2013; 21(10). PMID 23249954
58. Bozkurt B, Colvin M, Cook J, et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association. Circulation. Dec 06 2016; 134(23): e579-e646. PMID 27832612
59. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. Sep 2018; 20(9): 899-909. PMID 29904160
60. 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): 1308-39. PMID 21787999
61. Hershberger RE, Givertz MM, Ho CY, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. May 2018; 24(5): 281-302. PMID 29567486

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - 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 (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81405	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)
	81406	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)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	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)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

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

Effective Date	Action
04/30/2015	BCBSA Medical Policy adoption
03/01/2016	Policy revision without position change
02/01/2017	Coding update
04/01/2017	Policy revision without position change
02/01/2018	Coding update
04/01/2018	Policy revision without position change
07/01/2019	Policy title change from Genetic Testing for Dilated Cardiomyopathy. Policy revision with position change.
10/01/2025	Policy reactivated. Previously archived from 04/01/2020 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of

services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health

services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
Reactivated Policy Policy Statement: N/A	Genetic Testing for Idiopathic Dilated Cardiomyopathy 2.04.114 Policy Statement: I. 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**. II. 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**. III. Genetic testing for dilated cardiomyopathy is considered **investigational** in all other situations.