



# Louisiana

## Genetic Testing for Dilated Cardiomyopathy

**Policy #** 00409

Original Effective Date: 03/19/2014

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*Note: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy is addressed separately in medical policy 00270.*

*Note: Genetic Testing for Cardiac Ion Channelopathies is addressed separately in medical policy 00408.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for dilated cardiomyopathy (DCM) to be **investigational\*** in all situations.

### **Background/Overview**

#### **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. The age of onset for DCM is variable, ranging from infancy to the eighth decade, with most individuals developing symptoms in the fourth through sixth decades.

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

Many underlying conditions can cause DCM, including:

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

Therefore, when a patient presents with DCM, a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of clinical exam, blood pressure monitoring, electrocardiography (ECG), echocardiography, and workup for CAD as warranted by risk factors. In many

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cases, a definite underlying cause is not identified. Extensive workup including cardiac magnetic resonance imaging, exercise testing, right-sided catheterization with biopsy, and 24-hour ECG monitoring will uncover only a small number of additional etiologies for DCM. Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for secondary causes.<sup>3</sup> This has traditionally been termed *idiopathic dilated cardiomyopathy* (IDC).

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

Treatment 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 (AICD). AICD placement for primary prevention also may be performed if criteria for low ejection fraction and/or other clinical symptoms are present. End-stage DCM can be treated with cardiac transplantation.

### **Genetic DCM**

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

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

There may be interactions between genetic and environmental factors that lead to the clinical manifestations of DCM. A genetic variant may not in itself be sufficient to cause DCM, but may predispose to developing DCM in the presence of environmental factors such as nutritional deficiencies or viral infections.<sup>2</sup> It also has been suggested that DCM genetics may be more complex than simply single-gene variants, with low-penetrance variants that are common in the population contributing to a cumulative risk of DCM that includes both genetic and environmental factors.

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### **Genetic Testing for DCM**

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

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). No genotyping tests were identified. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

#### **Centers for Medicare and Medicaid Services (CMS)**

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

### **Rationale/Source**

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (i.e., a demonstration that the diagnostic information can be used to improve patient health outcomes).

## **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 prophylactic placement of a pacemaker and/or implantable cardioverter defibrillator (ICD) is sometimes considered in patients with DCM and *LMNA* or desmin (*DES*) disease-associated variants.

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

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

### Patients

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

### Interventions

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

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

Laboratory	Panel Name	No. of Genes Tested	Testing Method
Ambry Genetics	DCM panel	36	NGS
GeneDX	• DCM/Left Ventricular Non-Compaction Panel	61	CGH/NGS
	• Cardiomyopathies Del/Dup Panel	20	CGH
	• Cardiomyopathy Panel	91	CGH/NGS
Transgenomic	• DCM panel	13	Sanger sequencing
	• Conduction disease-DCM Panel	2	Sanger sequencing
Partners Healthcare	DCM/Arrhythmogenic Cardiomyopathy Panel	53	NGS
Baylor COM	DCM panel	52	NGS

COM: College of Medicine; DCM: dilated cardiomyopathy; CGH: comparative genomic hybridization; NGS: next-generation sequencing.

### 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

The general outcomes of interest are overall survival (OS), symptoms, change in disease status, functional outcomes, quality of life (QOL), and treatment-related morbidity. Specific outcomes in each of these categories are listed in Table 2.

The potential beneficial outcomes of primary interest would be improvement in OS and change in disease status because changes in management in symptomatic DCM are initiated to prevent sudden cardiac death

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and slow or reverse progression of heart failure. Improvement in symptoms, functioning, and QOL are also important.

Potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse effects from that treatment, in this case placement of ICD.

**Table 2. Outcomes of Interest for Individuals With Symptomatic DCM**

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
QOL	KCCQ, Minnesota Living with Heart Failure or other validated QOL assessment tools
Treatment-related morbidity	Adverse effects of implantable cardioverter defibrillator

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

### **Time**

Trials of genetic testing or treatment strategies in this population were not found. Two trials of ICD use in other nonischemic cardiomyopathies have reported that changes in 2- and 5-year OS 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 is complex. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### **Analytic Validity**

Analytic validity is the ability of a test to accurately and reliably measure the marker of interest. Measures of analytic validity include sensitivity (detection rate), specificity (1– false-positive rate), precision (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables). Analytic validity must be demonstrated in multiple sites and across populations of interest.

Commercially available genetic testing for DCM involves a variety of methods such as chip-based oligonucleotide hybridization, direct sequencing of protein-coding portions and flanking regions of targeted exons, and next-generation sequencing (NGS). Analytic validity is highest for direct sequencing, approaching 100%. For other methods of genetic testing, analytic validity may be lower and less precisely defined. For genomic hybridization and NGS, analytic sensitivity is in the range of 95% to 99%.

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In an NGS study, Haas et al (2015) achieved 50-fold coverage in 99.1% of 84 genes sequenced (i.e., each gene was sequenced at least 50 times). In a subsample of 25 gene segments containing at least 1 variant by Sanger sequencing, the sensitivity and specificity of NGS were 96% and 100%, respectively.

### Section Summary: Analytic Validity

The analytic validity of genetic testing for DCM is expected to be high when testing is performed by direct sequencing or NGS. However, published data for analytic validity of commercially available genetic tests is lacking.

### Clinical Validity

Numerous studies have evaluated the proportion of patients with clinically diagnosed DCM who have disease-associated variants. These studies vary in the genes examined and methods used to detect these variants. A common type of study describes the presence of 1 type of disease-associated variants in probands with DCM or family members of the proband. Fewer studies have evaluated multiple genes in cohorts of patients with DCM. In addition, only a limited number of studies have used 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).

### Next-Generation Sequencing

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

**Table 3. Studies Evaluating Clinical Validity of Genetic Testing for DCM With NGS**

Study (Year)	Population	Sequencing Method	Genes Tested	Results
Haas et al (2015); INHERITANCE	639 patients with sporadic (51%) or familial (49%) DCM	NGS	84 genes	<ul style="list-style-type: none"> <li>Known DCM-causing variants found in 101 (16%) patients</li> <li>Likely pathogenic variants found in 147 (23%) patients</li> <li>More than 1 DCM-associated variants in 82 (13%) patients</li> </ul>
Dalin et al (2017)	176 unrelated patients with idiopathic DCM and 503 healthy reference individuals from European ancestry cohort	NGS	41 DCM-related genes	<ul style="list-style-type: none"> <li>Fifty-five (31%) patients had 1 variant</li> <li>24 (14%) patients had ≥2 variants</li> </ul>
Pugh et al (2014)	766 patient with idiopathic DCM	NGS	Panels ranging from 5-46 genes	<p>As number of genes tested increased:</p> <ul style="list-style-type: none"> <li>Clinical sensitivity increased from 10% to 37%</li> <li>Inconclusive cases increased from 5% to 51%</li> </ul>

DCM: dilated cardiomyopathy; NGS: next-generation sequencing.

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The largest study to date, the European INHERITANCE (INtegrated HEart Research In TrANslational genetics of dilated Cardiomyopathies in Europe) project examined a comprehensive set of disease-associated variants and used NGS as the testing method. A total of 639 patients with sporadic (51%) or familial (49%) DCM were enrolled in 8 clinical centers in Europe between 2009 and 2011. Secondary DCM was ruled out by excluding patients with hypertension, valve disease, and other loading conditions; CAD 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/deletions, stop-gain/stop-loss variants, and splice-site variants); potential (not common, nonsynonymous variants associated with “disease” prediction according to online calculator, SNPs&GO); or benign (identified in the SNP database with allele frequency  $\geq 1\%$ ). 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 to 503 healthy reference individuals in the European ancestry cohort of the 1000 Genomes project. Fifty-five (31%) patients had 1 variant in the analyzed genes and 24 (14%) patients had 2 or more variants. Genetic variants in any gene, or variants in *LMNA*, *MYH7*, or *TTN* alone, were all associated with early disease onset and reduced transplant-free survival. *LMNA* variants had the strongest association with transplant-free survival. There was no difference in the prevalence of familial DCM between patients with and without variants. Patients with more than 1 variant were more likely to have familial DCM or potential familial DCM compared to patients with only 1 variant ( $p=0.046$ ). Stopgain and frameshift variants were more common in DCM patients (12%) than in the healthy reference individuals (0.6%). However, the prevalence of missense variants was 35% DCM patients and 37% healthy reference individuals; conservation and pathogenicity scores, and localization of missense variants were also similar in the 2 groups.

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

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### **Other Sequencing Methods**

Hirtle-Lewis et al (2013) used whole-exome sequencing of 4 genes as part of a strategy to identify and classify genetic variants associated with DCM. The population comprised 96 patients with idiopathic DCM treated at a Canadian clinic. The 4 genes examined were *LMNA*, *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 judged to have a high probability of causing disease, 4 were judged to be VUS, with the remainder considered benign.

The remaining studies have used older testing methods and 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 6 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 possibly (n=21) or unlikely (n=4) pathogenic.

In 2011, Millat et al 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*, *LMNA*, *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.

In 2012, Lakdawala et al studied 264 unrelated adult and children with DCM, approximately half of whom had familial disease. Ten genes (*MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *MYBPC3*, *ACTC*, *LMNA*, *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%), *LMNA* (5.3%), and *TNNT2* (3.7%). VUS were identified in an additional 10.6% (28/264) of individuals.

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 variant 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 *LMNA* variant carriers, 32% were diagnosed with DCM.

### **Commercially Available Tests**

For the evaluation of the clinical validity of a specific, commercially available test, studies that meet the following eligibility criteria would be considered:

- Reported on the accuracy of the marketed version of the test (including any algorithms used to calculate scores, if applicable);

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- Included a suitable reference standard (i.e., clinically diagnosed DCM);
- Patient/sample clinical characteristics were described and matched the patient characteristics listed in the PICOTS above; and
- Patient/sample selection criteria were described.

No such studies for any of the commercially available panels listed in Table 1 were identified.

### **Section Summary: Clinical Validity**

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

### **Clinical Utility**

Potential clinical utility 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.

To demonstrate clinical utility, results of genetic testing should be associated with changes in management that lead to improved outcomes. Changes in management could include initiation of therapy in a patient in whom the diagnosis is confirmed, and/or changes in screening or surveillance for at-risk family members.

### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. No such trials were identified.

### **Chain of Evidence**

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

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

The diagnosis of DCM is made on clinical grounds, requiring the presence of left ventricular enlargement and evidence of systolic dysfunction. The presence or absence of a disease-associated variant will not alter the clinical diagnosis of DCM. Genetic testing may influence the diagnostic workup for the underlying etiology of DCM. In patients with a likely familial component, genetic testing may improve the efficiency of

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workup by avoiding other tests for secondary causes of DCM likely to be negative. However, many of these tests (i.e., testing for thyroid disease, diabetes, echocardiography) are simple and noninvasive. Coronary angiography to rule out CAD still may be necessary in patients with a DCM-associated variant, depending on age and other risk factors for CAD. Therefore, the impact of genetic testing on the efficiency of workup is unknown. In patients with sporadic forms of DCM, testing for secondary causes will likely still precede genetic testing, so that genetic testing will not influence the diagnostic workup. Current treatment for DCM does not vary according to whether a disease-associated variant is present.

Although researchers have investigated pharmacogenetic associations in DCM, the absence of prospective, randomized trials to compare standard treatment to genotype-guided treatment precludes assessment of clinical utility of the findings. Reddy et al (2015) evaluated the impact of adrenergic receptor genotype on hemodynamic status in 2 cohorts of pediatric patients (age <22 years) who had DCM and stable (n=44) or advanced (i.e., listed for transplantation; n=91) heart failure. Three adrenergic receptor variants associated with heart failure in adults were genotyped: *ADRA2C* del322-325, *ADRB1* Gly389Arg, and *ADRB2* Gly16Arg. At mean follow-up of 2.2 years, patients with stable or advanced heart disease who had at least 1 variant showed greater response to  $\beta$ -blocker treatment than patients who had no variant (genotype  $\times$   $\beta$ -blocker interaction p values  $\leq 0.05$  for several hemodynamic parameters). Wasielewski et al (2014) investigated whether familial DCM may predispose to anthracycline-associated cardiomyopathy (AACM). Genotyping of 48 cardiomyopathy-associated genes in patients with DCM who also had AACM (n=5) and in patients with AACM alone who met criteria for familial DCM based on family history (n=6) identified 2 known pathogenic variants and 9 VUS. Because the intent of the study was descriptive, the statistical significance of these results was not determined.

### **Section Summary: Clinical Utility**

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

## **TESTING ASYMPTOMATIC INDIVIDUALS TO DETERMINE FUTURE RISK**

### **Clinical Context and Test Purpose**

The purpose of genetic testing for patients who are asymptomatic with a close relative who has DCM and a known genetic variant is to inform decisions regarding frequency of screening and timing of initiation of treatment such as when to implant a cardioverter defibrillator or start therapy with  $\beta$ -blockers or angiotensin-converting enzyme (ACE) inhibitors.

The 2009 Heart Failure Society of America guidelines on genetic evaluation of cardiomyopathy recommended screening of first-degree relatives of patients with DCM regardless of genetic testing. The guidelines recommended that asymptomatic first-degree relatives with negative findings for DCM be

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rescreened every 3 to 5 years, beginning in childhood or any time symptoms or signs appear and first-degree relatives with abnormal clinical screening suggestive of or consistent with DCM be rescreened every year. The guidelines also stated that an ICD may be considered at a higher threshold of left ventricular ejection fraction in patients with *LMNA* disease-associated variant.

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

It has been proposed that early initiation of therapy with ACE inhibitors or  $\beta$ -blockers may slow progression of heart failure but there is no evidence to support their use in asymptomatic patients.

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

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

### **Patients**

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

### **Interventions**

The interventions are the same as those listed in the previous section, but are 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**

The general outcomes of interest are morbid events, symptoms, functional outcomes, QOL, and treatment-related morbidity. Specific outcomes in each of these categories are listed in Table 4.

The potential beneficial outcome of primary interest would be reduction in incidence of morbid events because changes in management in symptomatic DCM are initiated to prevent development of heart failure and tachycardia. Prevention of symptoms, maintenance of functioning, and QOL are also important.

Potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse effects from that treatment, in this case placement of ICD or treatment with ACE inhibitors or  $\beta$ -blockers. False-negative test results could lead to delay in diagnosis and treatment.

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

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 $\beta$ -blockers

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

### **Time**

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 many years to become evident. Ten-year differences in 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.

### **Analytic Validity**

The evidence on analytic validity is as described in the previous section.

### **Clinical Validity**

Several studies have described the prevalence of DCM in family members of patients diagnosed with idiopathic DCM, with estimates ranging from 20% to 35%. However, studies on the yield of targeted genetic testing in family members are limited. Brodt et al (2013) evaluated 103 family members of patients with DCM from 16 pedigrees previously identified to carry *LMNA* familial variants. Sixty-four (62%) family members carried their familial *LMNA* variant, and 51 (79%) of those had ECG 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 ECG abnormalities at initial screening later developed DCM; the ECG abnormalities preceded DCM by a median of 7 years.

### **Clinical Utility**

In family members of patients with DCM, genetic testing can be used to determine if a known pathogenic variant has been inherited. Several issues in predictive testing for DCM create challenges for establishing clinical utility.

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This first requires confidence that the variant identified in the proband causes DCM (clinical validity). 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. 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. However, it is uncertain whether this approach leads to improved outcomes because of the uncertain clinical validity of testing. For example, a proband may be identified with a variant that is possibly pathogenic. A close family member may test negative for that variant and be falsely reassured that they are not at risk for DCM when they still may have another undiscovered variant.

Current surveillance and early treatment for DCM do not vary according to whether a disease-associated variant is present. 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 such trials are 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 effects of those treatments) and false-negative test results (delay of treatment initiation) need to be considered.

### **Section Summary: Clinical Utility**

It is uncertain how knowledge of a specific familial variant improves outcomes for asymptomatic individuals. Clinical guidelines supporting increased surveillance apply to individuals with a close family member regardless of genetic testing. Initiation of treatment is based on clinical findings. Early treatment based on a genetic diagnosis is unproven.

### **SUMMARY OF EVIDENCE**

For individuals who have signs and/or symptoms of DCM who receive comprehensive genetic testing, the evidence includes case series reporting analytic and clinical validity. Relevant outcomes are OS, change in disease status, test accuracy and validity, symptoms, functional outcomes, QOL, and treatment-related morbidity. The analytic validity of genetic testing for DCM is expected to be high when testing is performed by direct sequencing or NGS. In contrast, there is a large degree of uncertainty with clinical validity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 50%. Clinical specificity of DCM-associated variants is unknown, but DCM-associated variants in the same genes have been reported in 1% to 3% of patients without DCM. Because of the suboptimal clinical validity, the accuracy of assigning variants as disease-associated or benign may also be suboptimal. The clinical utility of genetic testing for diagnosing DCM has not been demonstrated.

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For a patient who is diagnosed with idiopathic DCM, the presence of a DCM-associated variant will not change treatment or prognosis. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who are asymptomatic with a first-degree relative who has DCM and a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes case series reporting analytic and clinical validity. Relevant outcomes are test accuracy and 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. However, it is uncertain how knowledge of a familial variant improves outcomes for an asymptomatic individual. The uncertain clinical validity of predictive testing makes it unclear whether actions taken as a result of testing will improve outcomes. Early treatment based on a genetic diagnosis is unproven. The evidence is insufficient to determine the effect of the technology on health outcomes.

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### **Policy History**

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03/06/2014 Medical Policy Committee review

03/19/2014 Medical Policy Implementation Committee approval. New policy.

01/01/2015 Coding Update

03/05/2015 Medical Policy Committee review

03/20/2015 Medical Policy Implementation Committee approval. No change to coverage.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

03/03/2016 Medical Policy Committee review

03/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update

03/02/2017 Medical Policy Committee review

03/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

03/01/2018 Medical Policy Committee review

03/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 03/2019

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Code Type	Code
CPT	81403, 81405, 81406, 81407, 81439, 81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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