Medical Policy

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Title: Genetic Testing for Dilated Cardiomyopathy

Description/Background

Dilated Cardiomyopathy

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

Idiopathic Dilated Cardiomyopathy

When a patient presents with DCM, a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. Extensive workup including cardiac magnetic resonance imaging (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 secondary causes listed above.[4] This has traditionally been termed IDC.

Clustering of IDC within families has been reported, leading to the conclusion that at least some cases of DCM have a genetic basis. Familial DCM is diagnosed when 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 (total nN=8097 patients) 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 (DCM)

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 may also lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope or sudden cardiac arrest.

Many underlying conditions that 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 (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 Testing for DCM
Approximately 30%-40% of patients with DCM who are referred for genetic testing will have a disease-associated variant identified.[5] 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-ropomysin (*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.[2] 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.

Regulatory Status

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. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The effectiveness of *targeted* genetic testing of the *LMNA, MYH7, TNNT2 and SCN5A* genes for familial dilated cardiomyopathy has been established. This testing is a useful diagnostic option for individuals meeting selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Targeted genetic testing for familial dilated cardiomyopathy (DCM) for the *LMNA, MYH7*, *TNNT2* and *SCN5A* genes is appropriate for:

- *Pre-symptomatic* individuals (no indications of left ventricular enlargement and dilatation in conjunction with significant systolic dysfunction or symptoms of heart failure) who do not meet the clinical features of idiopathic dilated cardiomyopathy but who have
  - A close relative (i.e., a first or second-degree relative) with a known genetic mutation for DCM, or
  - A close relative (i.e., a first or second-degree relative) diagnosed with idiopathic DCM by clinical means whose genetic status is unknown or unable to be obtained.
- *Symptomatic* individuals with significant cardiac conduction disease (e.g., first, second or third degree AV block) and/or who have been diagnosed with DCM and have two or more close relatives diagnosed with idiopathic DCM.

In addition to the above,

- The genetic testing should preferably be ordered by a specialist in cardiology or genetics.

- It is strongly recommended that genetic counseling be done in conjunction with genetic testing. The counselor will evaluate medical problems or risks present in a family, analyze and explain an inheritance pattern of any disorders found, provide information about the management and treatment of these disorders, and discuss available treatment options with the family or individual.

Exclusions:
- Genetic testing for any genes other than the *LMNA, MYH7, TNNT2* and *SCN5A* genes
- Next-generation sequencing panels
- Patients not meeting the above selection criteria.
- Genetic screening in the general population in absence of symptoms or family history of DCM

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81406 81407

Other codes (investigational, not medically necessary, etc.):

81403 81405 81439

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms are better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

TESTING PATIENTS WITH SIGNS AND/OR SYMPTOMS OF DILATED CARDIOMYOPATHY (DCM)

Clinical Context and Test Purpose

The purpose of genetic testing in individuals 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 is sometimes considered in patients with DCM and LMNA or desmin (DES) disease-associated variants.

The following **PICOs** were used to select literature to inform this review.

Populations

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.[7]

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 DCM patients 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
QOL	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 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 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 implantable cardioverter defibrillator (ICD).

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.

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).

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

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 variants 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.[20-22] 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 explained in more detail below.

Table 2. Studies Evaluating the Clinical Validity of Genetic Testing for DCM Using NGS

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 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 70genes	• 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 secondhighest (8%)
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 variants in 82 (13%) patients
Dalin et al (2017)[25]	176 unrelated patients with idiopathic DCM and 503 healthy reference individuals from European Ancestry cohort	NGS	41 DCM-related genes	• 55 (31%) patients had 1 variant • 24 (14%) patients had ≥2 variants
Pugh et al (2014)[27]	766 patients with idiopathic DCM	NGS	Panels ranging from 5-46 genes	As number of genes tested increased: • Clinical sensitivity increased from 10% to 37% • Inconclusive cases increased from 5% to 51%

DCM: dilated cardiomyopathy; NGS: next-generation sequencing

The largest study to date, the European INHERITANCE (INtegrated HEart Research In TrANslational genetics of dilated Cardiomyopathies in Europe) project (Hass et al, 2015), examined a comprehensive set of disease-associated variants and used NGS as the testing method.[23] A total of 639 patients with sporadic (51%) or familial (49%) DCM were enrolled in 8clinical 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[29] 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 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. TTN was the largest contributor to positive test results (14%); LMNA 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.[30] 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 categorized as clinically significant variants which lead to deletions or truncations, altering proteins which would result in a high probability of causing disease. Four were judged to be variants of uncertain significance (VUS), with the remainder considered benign.

In 2017, van der Linde et al published a retrospective analysis of 80 individuals (15 probands, 65 family members) in the Netherlands who had a variant in the *MYH7* gene identified through whole exome sequencing.[31] 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 that the sample size and length of follow-up were not optimal and could not account for other potential genetic factors.

Myers et al (2018) evaluated the presence of Bcl2-associated anthanogene 3 (BAG3) variants in African Americans with dilated cardiomyopathy and the association of the variants on event-free survival.[32] 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=0.02).

Verdonschot et al (2018) compared long term outcomes among DCM patients with (n=38) and without (n=265) truncating titin variants (TTNtv).[33] 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 (LTA), and unscheduled heart failure hospitalizations. None of the outcomes was significantly different among patients with and without TTNtv except for LTA. Patients with TTNtv experienced significantly more LTA compared with patients without TTNtv (hazard ratio: 2.8; 95% 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 (hazard ratio: 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.[34] 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=0.005). 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=0.007) and 28 (29%) patients died (51% pathogenic variant-positive vs. 15% pathogenic variant-negative; p<0.001).

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.

In 2011, Millat et al examined a cohort of 105 unrelated patients with DCM.[35] 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.[36] 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 small Slovakian study by Priganc et al (2017) screened 58 patients with DCM or hypertrophic cardiomyopathy for variants in exons 12, 20, or 21 of *SCN5A* gene; also included were 26 healthy individuals.[37] Of the 10 missense variants found, three were judged to be pathogenic (*T12471*, *A1260D*, *G1262S*); however, given that the incidence of the variants was mixed between case and control cohorts, there was no clear association between disease and the presence of a variant. Roughly one-third (32.76%) of the patients with DCM or hypertrophic cardiomyopathy did not show any variant in the *SCN5A* gene; this result and the small size of the study made conclusions uncertain.

A few studies have documented the range of diagnoses (i.e., lack of specificity) associated with DCM-associated variants. In the Netherlands, the PLN (phospholamban) *R14del* variant is a founder 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.[38] In another 2014 retrospective cohort of 41 symptomatic and asymptomatic LMNA variant carriers, 32% were diagnosed with DCM.[39]

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

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.

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

Chain of Evidence
There are no randomized controlled trials assessing clinical utility. Below are discussions of 2 prospective observational studies.

In an observational prospective study, Hasselberg et al (2017) followed 79 individuals with a lamin A/C variant (LM) who were either symptomatic probands (n=48) or asymptomatic

genotype-positive family members (n=31).[40] By the end of 4 years follow-up, 37% of the patients were pacemaker dependent due to third degree atrioventricular blockage. During an average of 8 years of follow-up, 15 of the 79 probands received heart transplantations. Asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) of cardiac penetrance during an average of 4 years of follow-up. Given the combined likelihood of morbidity and mortality, the requirement for heart transplantation, and the considerable frequency of other cardiac events observed during follow-up in both symptomatic and asymptomatic groups, the investigators recommended that relatives of probands with known LM variant be screened due to increased risk.

Although researchers have investigated pharmacogenetic associations in DCM, the absence of prospective, randomized trials to compare standard treatment 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.[41] Three adrenergic receptor variants associated with heart failure in adults were genotyped: *ADRA2C del322-325, ADRB1 Gly389Arg, and ADRB2 Gly16Arg*. At mean follow-up of 2.2 years, patients with stable or advanced heart disease who had at least 1 variant showed greater response to β-blocker treatment than patients who had no variant (genotype x β-blocker interaction p values ≤0.05 for several hemodynamic parameters). Wasielewski et al (2014) investigated whether familial DCM may predispose to anthracycline-associated cardiomyopathy (AACM).[42] 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.

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 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 (ACE) inhibitors.

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

The following **PICOs** were 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. 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.

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. Patients who have a relative with DCM are screened and treated by a primary care physician or cardiologist in an outpatient clinical setting.

Outcomes
Specific outcomes are listed in Table 3.

Table 3. Outcomes of Interest for Asymptomatic Individuals with a Relative with DCM

Outcomes	Details
Morbid events	Incidents 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; DCM: dilated cardiomyopathy; 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 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.

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 20% to 35%.[43-46] Brodt et al (2013) conducted a study of 64 (62%) family members identified as carrying the LMNA variant.[47] Fifty-one (79%) of the patients had electrocardiographic abnormalities at initial screening (mean age of onset, 41 years; range, 18-76 years). Twenty-six (25%) had ventricular dysfunction (mean age of onset, 48 years; range, 28-82 years), and 11 (11%) had DCM. Sixteen family members with electrocardiographic abnormalities at initial screening later developed DCM; the electrocardiographic abnormalities preceded DCM by a median of 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.[48] 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 from2006 to 2020 at a regional assembly of clinics for inherited cardiomyopathies in Denmark.[49] At baseline, 124relatives (22%) were diagnosed with familial DCM. During a median follow-up of 5.0 years, an additional 45individuals 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.[50] 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 (see Table 4).

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

Study	Population	SequencingType	GeneTested	Results
Huggins et al(2022)[48]	Patients with DCM(n=1220 probands)and their first-degree relatives(n=1693)	Exomesequencing	NR	The crude prevalence of familial DCMamong probands was 11.6% A model-based estimate of DCM riskby age 80 years in first-degreerelatives was 19% A model-based estimate of theprevalence of familial DCM amongprobands if all living first-degreerelatives were screened was 29.7%(95% CI, 23.5% to 36.0%)
Stava et al (2022)[50]	Patients with DCM(n=1541 probands)and their relatives(n=1045)	Sangersequencing (until 2015);Sangersequencingand/or NGS(since 2015)	Multiple	Data from 4408 cardiomyopathyprobands identified a 14.1% hit-rate forDCM 44.1% of the relatives were positive fora variant previously found in theirfamily The most common DCM variant inprobands and relatives combined wasthe c.40_42del variant in *PLN*,accounting for 19% of all DCM variants
Vissing et al (2022)[49]	211 families withinheritedcardiomyopathies(n=563)	NR	Multiple	At baseline, 124 individuals (22%)were diagnosed with familial DCM During a median follow-up of 5.0years, an additional 45 individualsdeveloped DCM, increasing the overallyield to 34%
Fernlund et al(2017)[51]	11-mo probandwith DCM and 6family 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)[52]	6 members of afamily with ahistory of CHF	NGS	*δ-Sg*	2 individuals had a heterozygous variant (p.R97Q)in *δ-Sg* gene; the variant was not found in 100controls
Bodian et al (2017)[53]	Infant proband withintractablediarrhea and DCM	WGS	*EPCAM*	The *EPCAM*-variant (c.556-14A>G) suggestsintestinal tufting, but this condition was notobserved
Yuan et al (2017)[54]	Proband and 4family memberswith DCM and/orarrhythmia	WES	*KCNJ12*	Of 12 shared variants identified, the*KCNJ12*variant (p.Glu334del) did not appear inEuropean or African registries

Petropoulou et al(2017)[55]	Proband and 1family memberwith atypical DCM	WES	*TNNT2*,*MYH7*	Variants found (c.247A>C; p.Asn83His in *TNNT2*;c.2863G>A; p.Asp955Asn in *MYH7*) wereassessed as potentially damaging or disease-causing; a third variant in *PRDM16*wasinconclusively associated with cardiomyopathy
Rafiq et al (2017)[56]	3 members of afamily with historyof DCM	WES	*BAG3*	4 other members were described butnot tested Tested individuals showed BAG3 variant (Chr10:121435979-delC
Liu et al (2017)[57]	Family 1: probandand 5 familymembers withDCM Family 2:asymptomaticproband and 4family memberswith DCM	WES	*TTN*	Family 1: Nonsense variant(c.12325C>T/p.R4109X) assessed asdisease-causing and -damaging Family 2: Missense variant(c.17755G.C/p.G5919R) absent incontrol cohort

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

Clinically Useful

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

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

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

Uncertain penetrance and variable clinical expression also need to be considered in determining the utility of predictive testing.[58] 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.[58] 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.

In the observational prospective study by Hasselberg et al (2017) described above, 31 of the 79 individuals were asymptomatic family members with a lamin A/C variant (LM).[40] The asymptomatic family members experienced a 9% annual incidence of newly documented cardiac phenotype and 61% (19/31) of cardiac penetrance during an average of 4 years of follow-up. Ten (31%) experienced atrioventricular blockage, 12 experienced ventricular tachycardia, and 7 experienced atrial 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 LM variant be screened.

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

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.

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 1known 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.

SUPPLEMENTAL INFORMATION

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 a scientific statement from the American Heart Association (AHA) in 2016 regarding diagnostic and treatment strategies for specific DCM, the AHA states that "A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies."[59]

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

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

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 DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered.	C

I: is recommended; IIa: can be useful; 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.[60] The following recommendations were made for all types of cardiomyopathy:

a) Genetic testing is recommended for the most clearly affected family member.
b) Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
c) In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.

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

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

Heart Rhythm Society and European Heart Rhythm Association

The Heart Rhythm Society and European Heart Rhythm Association issued joint guidelines (2011) on genetic testing for cardiac channelopathies and cardiomyopathies.[61] These guidelines included following recommendations on genetic testing for DCM and was reaffirmed in 2018 (see Table 6).

Table 6. Genetic Testing Recommendations for DCM

Recommendation	COR
“Comprehensive or targeted (*LMNA and SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (i.e., first-, second-, or third-degree heart block) and/or with a family history of premature unexpected sudden death.”	I
“Mutation-specific [familial variant] testing is recommended for family members and appropriate relatives following the identification of a DCM-causitive 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; DCM: dilated cardiomyopathy

The Heart Rhythm Society and European Heart Rhythm Association (2011) consensus statement also noted that prophylactic implantable cardioverter defibrillator can be considered in patients with known arrhythmia and/or conduction system disease (*LMNA* or *Desmin* [*DES*]).[61]

Heart Failure Society of America

The Heart Failure Society of America (HFSA) published a practice guideline in 2018 on the Genetic Evaluation of Cardiomyopathy.[62] 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)."

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently 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			
NCT03037632	Precision medicine for dilated cardiomyopathy in European and African Ancestry	6500	Apr 2024
NCT01857856	PHOspholamban Related Cardiomyopathy Study-intervention (Efficacy study of eplerenone in presymptomatic PLN-R14del Carriers)	84	Mar 2024
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	Jul 2025
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			
NCT03572569	Risk Stratification in Children and Adolescents with Primary Cardiomyopathy	200	Dec 2020 (unknown)
NCT01736566	The MedSeq Project pilot study: integrating whole genome sequencing into the practice of clinical medicine	2213	Aug 2022 (ongoing)
NCT02148926	Clinical and genetic examinations of dilated cardiomyopathy	4554	Jun 2018

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

Government Regulations

National

There is no national coverage determination on this topic.

Local:

Wisconsin Physicians Service Insurance Corporation [08202] – MI MAC Part B (J8) - Local Coverage Article for MolDX: Excluded Test List, A55247(Rev. Eff. 02/16/2017). Retired 01/01/2018.

Excluded Test List

After a review of the current available literature, WPS GHA has determined that testing for the following genes/gene components does not meet the Medicare criteria for a covered service.

CPT Code	Descriptor
81403	PLN
81405	ANKRD1
81405	TPM1
81405	TNNC1
81406	LDB3
81406	LMNA
81406	TNNT2
81407	MYH6
81407	MYH7
81407	SCN5A

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing for Cardiac Channelopathies
- Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/14	4/8/14	5/12/14	Joint policy established
11/1/15	8/24/15	9/14/15	Routine maintenance
9/1/16	6/21/16	6/21/16	Routine maintenance, updated rationale and references. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance Genetics nomenclature updated throughout policy References and rationale updated CPT code 81439 added for panel test
9/1/18	6/19/18	6/19/18	Updated rationale, added references 29, 33-34, and 46-54. No change in policy status.
9/1/19	6/18/19		Rationale updated, reference # 33, 57 and 58 added. No change in policy status.
9/1/20	6/16/20		Routine policy maintenance, no change in policy status.
9/1/21	6/15/21		Routine policy maintenance, added reference #31. No change in policy status.
9/1/22	6/21/22		Routine policy maintenance, no change in policy status.
9/1/23	6/13/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
9/1/24	6/11/24		Rationale updated, references 23,24,48-50 added. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR DILATED CARDIOMYOPATHY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.