

## Corporate Medical Policy

### Genetic Testing for Dilated Cardiomyopathy

**File Name:** genetic\_testing\_for\_dilated\_cardiomyopathy  
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**Last CAP Review:** 10/2017  
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**Last Review:** 10/2017

#### Description of Procedure or Service

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Dilated cardiomyopathy (DCM) is characterized by progressive left ventricular enlargement and systolic dysfunction, leading to clinical manifestations of heart failure. There are a variety of causes of DCM, which include genetic and non-genetic conditions. Genetic forms of DCM are heterogeneous in their molecular basis and clinical expression. Genetic testing for DCM has potential utility in confirming a diagnosis of genetic DCM, and as a prognostic test in family members when familial DCM is present.

Dilated cardiomyopathy (DCM) is defined as the presence of left ventricular enlargement and dilatation in conjunction with significant systolic dysfunction. Dilated cardiomyopathy has an estimated prevalence of 1 in 2700 in the US. The age of onset for DCM is variable, ranging from infancy to the eighth decade, with most individuals developing symptoms in the 4th through 6th decade.

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

There are many underlying conditions that can cause DCM, including:

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

Therefore, when a patient presents with DCM, a work-up is performed to identify underlying causes, especially those that are treatable. The standard workup consists of clinical exam, blood pressure monitoring, electrocardiography (ECG), echocardiography, and workup for coronary artery disease as warranted by risk factors. In many 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 35-40% of DCM cases are thus determined to be idiopathic after a negative workup for secondary causes. This has traditionally been termed idiopathic dilated cardiomyopathy (IDC).

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

Treatment of DCM is similar to 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 may also be treated with antiarrhythmic medications, pacemaker and/or an automatic implantable cardiac defibrillator (AICD). AICD placement for primary prevention may also be performed if criteria for low ejection fraction and/or other clinical symptoms are present. DCM that is end-stage can be treated with cardiac transplantation.

## Genetic DCM

Genetic DCM has been proposed as a newer classification that includes both familial dilated cardiomyopathy and some cases of sporadic IDC. The percent of patients with sporadic DCM that have a genetic basis is not well characterized. The majority of disease-associated variants are inherited in an autosomal dominant fashion, but some autosomal recessive, X-linked, and mitochondrial patterns of inheritance are also 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 and colleagues (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 the development of DCM in the presence of environmental factors such as nutritional deficiencies or viral infections. It has also 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.

## Genetic Testing for DCM

Approximately 30%-40% of patients who are referred for genetic testing will have a disease-associated variant identified. Disease-associated variants associated with DCM have been identified in over 40 genes of various types and locations. The most common genes involved are genes that code for titin (*TTN*), myosin heavy chain (*MYH7*), troponin T (*TNNT2*), and alpha-tropomyosin (*TPM1*). These four 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.

Genetic testing can be performed on any of a 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.

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Because of the large number of potential variants associated with DCM and the infrequent nature of most variants, panel testing is frequently offered. Some examples of genetic panels for DCM that are commercially available are provided in the following table.

**Table.** Commercially available genetic panels for DCM

Laboratory	Panel name	Number of genes tested	Testing method
Ambry Genetics	DCM panel	36	Next-gen sequencing
GeneDX	DCM/Left Ventricular Noncompaction Panel	61	CGH/Next-gen sequencing
	Cardiomyopathies Del/Dup Panel	20	CGH
	Cardiomyopathy panel	91	CGH/Next gen. sequencing
Transgenomic	DCM panel	13	Sanger sequencing
	Conduction disease-DCM Panel	2	Sanger sequencing
Partners Healthcare	DCM/Arrhythmogenic Cardiomyopathy Panel	53	Next-gen sequencing
Baylor COM	DCM panel	52	Next gen.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Related Policies:

Genetic testing for predisposition to inherited hypertrophic cardiomyopathy  
Genetic testing for cardiac ion channelopathies  
General approach to evaluation the utility of genetic panels

## Policy

**Genetic testing for dilated cardiomyopathy is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Genetic Testing for Dilated Cardiomyopathy is covered

Not applicable.

## When Genetic Testing for Dilated Cardiomyopathy is not covered

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

## Policy Guidelines

The evidence for comprehensive genetic testing for individuals with signs, and/or symptoms of dilated cardiomyopathy (DCM), include case series reporting analytic and clinical validity. Relevant outcomes are overall survival, change in disease status, test accuracy, test validity, symptoms, functional outcomes, treatment-related morbidity, and quality of life. Analytic validity of genetic testing for DCM is expected to be high when testing is performed by direct

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sequencing or next-generation sequencing. 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 10-50%. The clinical specificity of DCM-associated variants is not known, but DCM-associated variants in the same genes have been reported in 1-3% of patients without DCM. Because of the suboptimal clinical validity, the accuracy of assigning variants as disease-associated or benign may also be suboptimal. Clinical utility of genetic testing for diagnosing DCM has not been demonstrated. For a patient who is diagnosed with idiopathic DCM, the presence of a disease-associated variant will not change treatment or prognosis. The evidence is insufficient to determine the impact of the technology on health outcomes.

The evidence for targeted genetic testing in individuals who are asymptomatic with a first-degree relative who has dilated cardiomyopathy and a known familial variant includes, case series reporting analytic and clinical validity. Relevant outcomes are test accuracy and validity, symptoms, morbid events, functional outcomes, treatment-related morbidity, and quality of life. 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 creates uncertainty about 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 impact of the technology on health outcomes.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: Effective in 2017, there is a genomic sequencing panel (GSP) CPT code for inherited cardiomyopathy testing: 81439*

*If a GSP is performed that doesn't meet the criteria in code 81439, the following Tier 2 codes may be used: 81403, 81405, 81406, 81407*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 10/2017

Medical Director review 10/2017

## Policy Implementation/Update Information

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2/25/14 New policy implemented. Genetic testing for dilated cardiomyopathy is considered investigational in all situations. Medical Director review 2/25/14. Policy noticed 2/25/14 for effective date 4/29/14. (mco)

1/13/15 References updated. Specialty Matched Consultant Advisory Panel review 11/2014. Senior Medical Director review 11/2014. No change to Policy statements. (td)

# Genetic Testing for Dilated Cardiomyopathy

- 2/24/15 References updated. Policy Statement remains unchanged. (td)
- 12/30/15 References updated. Specialty Matched Consultant Advisory Panel review 10/29/2015. Medical Director review 10/2015. (td)
- 4/1/16 Description section updated. Policy Guidelines sections updated. References updated. (td)
- 11/22/16 Specialty Matched Consultant Advisory Panel review 10/2016. Medical Director review 10/2016. (jd)
- 12/30/16 Code 81439 added to Billing/Coding section. (jd)
- 5/26/17 Minor revisions with updated genetic terminology. Commercially Available Genetics Panel for DCM - table updated with current number of genes tested. References updated. Medical Director review 2/2017. (jd)
- 11/10/17 Specialty Matched Consultant Advisory Panel review 10/2017. Medical Director review 10/2017. (jd)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.