



Louisiana

Genetic Testing for Dilated Cardiomyopathy

Policy # 00409

Original Effective Date: 03/19/2014

Current Effective Date: 07/13/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider comprehensive genetic testing for individuals with signs or symptoms of dilated cardiomyopathy which is considered idiopathic after a negative workup for secondary causes to be **eligible for coverage**** (See Policy Guidelines).

Based on review of available data, the Company may consider targeted genetic testing for asymptomatic individuals with a first-degree relative who has dilated cardiomyopathy and a known familial variant to be **eligible for coverage.****

Note:

If there is an evidence that previous genetic testing for dilated cardiomyopathy was completed, repeated testing is not necessary and is not eligible for coverage.

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When 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 in all other situations to be **investigational**.*

Policy Guidelines

Standard Workup for Patients With Signs or Symptoms of Dilated Cardiomyopathy

The standard workup for patients with signs or symptoms of dilated cardiomyopathy includes a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for vitamin B1 deficiency and coronary artery disease as warranted by risk factors. Extensive workup including cardiac magnetic resonance imaging, exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in D and serves as an international standard in D diagnostics. It was implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

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Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the D sequence
	Variant	Change in the D sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the D sequence
Likely pathogenic	Likely disease-causing change in the D sequence
Variant of uncertain significance	Change in D sequence with uncertain effects on disease
Likely benign	Likely benign change in the D sequence
Benign	Benign change in the D sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at-risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Diagnosis of Dilated Cardiomyopathy

Primary clinical manifestations of dilated cardiomyopathy (DCM) are heart failure and arrhythmias. Symptoms of heart failure, such as dyspnea on exertion and peripheral edema, are the most common

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presentations of DCM. These symptoms are generally gradual in onset and slowly progressive over time. Progressive myocardial dysfunction also may lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope, or sudden cardiac arrest.

Many underlying conditions can cause DCM, including:

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

Treatment of Dilated Cardiomyopathy

Treatment of DCM is similar to that for other causes of heart failure. This includes medications to reduce fluid overload and relieve strain on the heart and lifestyle modifications such as salt restriction. Patients with clinically significant arrhythmias also may be treated with antiarrhythmic medications, pacemaker implantation, and/or an automatic implantable cardiac defibrillator. Automatic implantable cardiac defibrillator placement for primary prevention also may be performed if criteria for low ejection fraction and/or other clinical symptoms are present. End-stage DCM can be treated with cardiac transplantation.

Genetic Testing for Dilated Cardiomyopathy

Approximately 30% to 40% of patients with DCM referred for genetic testing will have a disease-associated variant identified. 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), alpha-tropomyosin (TPM1) and Lamin A/C gene (LMNA). 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.

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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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

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

For individuals who have signs and/or symptoms of DCM who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. Relevant outcomes are overall survival, test validity, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 40%. Additional studies assessed clinical outcomes of patients with DCM and at least 1 known variant compared with patients with DCM and no known variants. The studies reported that patients with DCM and known variants experienced lower event-free survival, earlier onset of symptoms, lower transplant-free survival, and more life-threatening arrhythmias compared with patients with DCM and no known variants. A prospective observational study has reported that patients with DCM and known variants experienced high rates of morbidity and mortality during 4 to 8 years of follow-up. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management which improve net health outcomes. Changes in management may include earlier implantation of cardiac defibrillators or increased surveillance to detect worsening of symptoms, as well as cascade genetic testing of asymptomatic family members. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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For individuals who are asymptomatic with a first-degree relative who has DCM and a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes case series reporting clinical value and a prospective observational study reporting clinical utility. 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 a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

American Heart Association

In 2016, the American Heart Association (AHA) released a scientific statement regarding diagnostic and treatment strategies for specifically dilated cardiomyopathy (DCM), the AHA stated: "A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies." Table 1 summarizes the AHA recommendations regarding genetic testing for patients with DCM.

Table 1. Genetic Testing Recommendations for Dilated Cardiomyopathy by the American Heart Association

Recommendation	LOE
Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.	B
In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling.	B

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Recommendation	LOE
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 (ie, 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

DCM: dilated cardiomyopathy; LOE: level of evidence.

American College of Medical Genetics and Genomics

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

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

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

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

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Heart Rhythm Society and European Heart Rhythm Association

In 2011, the Heart Rhythm Society and European Heart Rhythm Association issued joint guidelines on genetic testing for cardiac channelopathies and cardiomyopathies. These guidelines included the following recommendations on genetic testing for DCM (see Table 2).

Table 2. Genetic Testing Recommendations for DCM by the Heart Rhythm Society and European Heart Rhythm Association

Recommendation	COR
“Comprehensive or targeted (LM and SCN5A) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) and/or with a family history of premature unexpected sudden death.”	I
“Mutation-specific [familial variant] testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.”	I
“Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.”	IIa

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

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

Heart Failure Society of America

In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy. The following recommendations for genetic testing for cardiomyopathy (including DCM) were made:

- “Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered (Level of Evidence B).”
- “Genetic testing should be considered for the one most clearly affected person in a family to facilitate screening and management.”

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- “Genetic and family counseling is recommended for all patients and families with cardiomyopathy (Level of Evidence A).”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02148926	Clinical and Genetic Examinations of Dilated Cardiomyopathy	4554	Jun 2018
NCT03572569	Risk Stratification in Children and Adolescents with Primary Cardiomyopathy	200	Dec 2020
NCT03037632	Precision Medicine for Dilated Cardiomyopathy in European and African Ancestry	6500	Jun 2021
NCT01857856	PHOspholamban RElated CARDiomyopathy STudy - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)	182	Jul 2021
NCT01736566	The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine	2213	Aug 2022

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Unpublished			
NCT02057341 ^a	A Study of ARRY-371797 in Patients With LM-Related Dilated Cardiomyopathy	12	May 2016 (completed; updated 5/16/17)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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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.
- 06/06/2019 Medical Policy Committee review
- 06/19/2019 Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for Dilated Cardiomyopathy” to “Genetic Testing for Idiopathic Dilated Cardiomyopathy”. Policy statements changed from investigational to medically necessary. Added a *Note* after the second eligible for coverage statement as follows: “*If there is evidence that previous genetic testing for dilated cardiomyopathy was completed, repeated testing is not necessary and is not eligible for coverage.*” Added vitamin B1 deficiency to workup for patients with signs and symptoms of dilated cardiomyopathy in the Policy Guidelines.
- 06/04/2020 Medical Policy Committee review
- 06/10/2020 Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for Idiopathic Dilated Cardiomyopathy” to “Genetic Testing for Dilated Cardiomyopathy”. Coverage eligibility unchanged.

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Next Scheduled Review Date: 06/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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

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***Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary** (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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