BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.114 Genetic Testing for Idiopathic Dilated Cardiomyopathy

Effective Policy Date: July 1, 2023

Original Policy Date: March 2014

Related Policies:

2.04.43 - Genetic Testing for Cardiac Ion Channelopathies

Genetic Testing for Idiopathic Dilated Cardiomyopathy

Description

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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, 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.

OBJECTIVE

The objective of this evidence review is to examine whether genetic testing improves net health outcomes in individuals with suspected dilated cardiomyopathy and in asymptomatic individuals who have a relative with dilated cardiomyopathy and a known familial variant.

POLICY STATEMENT

Comprehensive genetic testing for individuals with signs or symptoms of dilated cardiomyopathy, which is considered idiopathic after a negative workup for secondary causes, is considered **medically necessary**.

POLICY GUIDELINES

Standard Workup for Patients With Signs or Symptoms of Dilated Cardiomyopathy

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

Genetics Nomenclature Update

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

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology<97>"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"<97>to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

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

Genetic Counseling

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

Summary of Evidence

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

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 2016, the American Heart Association (AHA) released a scientific statement regarding diagnostic and treatment strategies for specific dilated cardiomyopathy (DCM), the AHA stated: "A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies."[57,] 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
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 a DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered.	C

DCM: dilated cardiomyopathy; LOE: level of evidence.

American College of Medical Genetics and Genomics

In 2018, the American College of Medical Genetics and Genomics (ACMG) published clinical practice recommendations for the genetic evaluation of cardiomyopathy.[58,] The following recommendations were made for all types of cardiomyopathy:

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

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

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

Heart Rhythm Society and European Heart Rhythm Association

In 2011, the Heart Rhythm Society and European Heart Rhythm Association issued joint guidelines on genetic testing for cardiac channelopathies and cardiomyopathies.[59,] These guidelines included the following recommendations on genetic testing for DCM and were reaffirmed in 2018 (Table 2).

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

Recommendation	COR
"Comprehensive or targeted (*LM*and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (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]).[59,]

Heart Failure Society of America

In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy.[60,] The following recommendations for genetic testing for cardiomyopathy (including DCM) were made:

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2014	New policy	Genetic testing for dilated cardiomyopathy is considered investigational for all indications
March 2015	Replace policy	Policy updated with literature review; references 5, 18-19, and 21-25 added. Policy statement unchanged
June 2018	Replace policy	Policy updated with literature review through December 11, 2017; references 29, 33-34, and 46-54 added. Policy statement unchanged; summary of evidence updated to reflect FEP benefit application for "existing medical condition,
June 2019	Replace policy	Policy updated with literature review through December 4, 2018; several references added. Policy statements changed from investigational to medically necessary. Title changed to "Genetic Testing for Idiopathic Dilated Cardiomyopathy"
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statement unchanged.
June 2021	Replace policy	Policy updated with literature review through January 2, 2021; references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through December 17, 2021; no references added. Policy statement unchanged.
June 2023	Replace policy	Policy updated with literature review through December 9, 2022; references added. Policy statements unchanged.