FEP 2.04.114 Genetic Testing for Dilated Cardiomyopathy

Effective Date: July 15, 2018

Related Policies:
2.04.43 Genetic Testing for Cardiac Ion Channelopathies

Genetic Testing for Dilated Cardiomyopathy

Description

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.

FDA 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). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. 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.

POLICY STATEMENT

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

POLICY GUIDELINES

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 is being 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 Organization, 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.

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

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

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.

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

RATIONALE

Summary of Evidence

For individuals who have signs and/or symptoms of DCM who receive comprehensive genetic testing, the evidence includes case series reporting clinical validity. Relevant outcomes are overall survival, test accuracy and validity, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. There is a large degree of uncertainty with clinical validity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 50%. Clinical specificity of DCM-associated variants is unknown, but DCM-associated variants in the same genes have been reported in 1% to 3% of patients without DCM. Because of the suboptimal clinical validity, the accuracy of assigning variants as disease-associated or benign may also be suboptimal. The clinical usefulness of genetic testing for diagnosing DCM has not been demonstrated. For a patient diagnosed with idiopathic DCM, the presence of a DCM-associated variant will not change treatment or prognosis. The evidence is insufficient to determine the effect of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

British Society of Echocardiography

Guidelines from the British Society of Echocardiography (2017) have presented diagnostic criteria for assessing dilated cardiomyopathy (DCM) with echocardiography, recommending that caregivers regularly administer echocardiograms to individuals with potential genetic risk, particularly those related to an individual with idiopathic DCM.[53] The guidelines did not address the use of genetic testing in cases of DCM.

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.[55] These guidelines included following recommendations on genetic testing for DCM (see Table 1).

Table 1 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 (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; 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*]).[55]

Heart Failure Society of America

The Heart Failure Society of America published practice guidelines (2009) on the genetic evaluation of cardiomyopathy.[52] 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
March 2014	New Policy	Genetic testing for dilated cardiomyopathy is considered investigational for all indications
March 2015	Update Policy	Policy updated with literature review; references 5, 18-19, and 21-25 added. Policy statement unchanged.
June 2018	Update 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”.