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.

OBJECTIVE

The objective of this evidence review is to examine whether genetic testing improves net health outcomes in individuals with suspected dilated cardiomyopathy. This policy does not address 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 includes 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, 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 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>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
### Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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.

### 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).

### 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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 DCM who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. The relevant outcomes are overall survival, test validity, symptoms, change in disease status, functional outcomes, QOL, 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 one 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 four to eight 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.

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. The relevant outcomes are test validity, symptoms, morbid events, functional outcomes, QOL, 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 four to eight 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 a scientific statement from the AHA (2016) regarding diagnostic and treatment strategies for specific dilated cardiomyopathy (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." 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

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

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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.

**Recommendations for Pediatric DCM**

<table>
<thead>
<tr>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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.</td>
</tr>
<tr>
<td>B</td>
<td>Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.</td>
</tr>
<tr>
<td>A</td>
<td>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.</td>
</tr>
<tr>
<td>C</td>
<td>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.</td>
</tr>
</tbody>
</table>

**LOE: level of evidence**

### American College of Medical Genetics and Genomics

The ACMG (2018) 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

The Heart Rhythm Society and European Heart Rhythm Association (2011) issued joint guidelines on genetic testing for cardiac channelopathies and cardiomyopathies. These guidelines included the following recommendations on genetic testing for DCM (see Table 6).

Table 6. Genetic Testing Recommendations for DCM by the Heart Rhythm Society and European Heart Rhythm Association

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;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.&quot;</td>
<td>I</td>
</tr>
<tr>
<td>&quot;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.&quot;</td>
<td>I</td>
</tr>
<tr>
<td>&quot;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.&quot;</td>
<td>IIa</td>
</tr>
</tbody>
</table>

COR: class of recommendation (I: recommended; IIa: can be useful); 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 (LM or Desmin [DES]).

Heart Failure Society of America

The Heart Failure Society of America (2018) 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."
- "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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REFERENCES


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55. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011;8(8):1308-1339. PMID 21787999.


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FEP 2.04.114 Genetic Testing for Dilated Cardiomyopathy

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2014</td>
<td>New policy</td>
<td>Genetic testing for dilated cardiomyopathy is considered investigational for all indications.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review; references 5, 18-19, and 21-25 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>June 2018</td>
<td>Replace policy</td>
<td>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”.</td>
</tr>
<tr>
<td>June 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through December 4, 2018; several references added. Policy statements changed from investigational to medically necessary. Title changed to &quot;Genetic Testing for Idiopathic Dilated Cardiomyopathy&quot;</td>
</tr>
</tbody>
</table>