Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
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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.

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 to be investigational* in all situations.

Background/Overview
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 nongenetic 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 predictive test in family members when familial DCM is present.

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 U.S. The age of onset for DCM is variable, ranging from infancy to the eighth decade, with the majority of individuals developing symptoms in the fourth through sixth decade.

The 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 workup is performed to identify underlying causes, especially those that are treatable. In many cases, a definite underlying cause is not identified. Approximately 35% to 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).
Clustering of idiopathic DCM 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 2 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 idiopathic dilated cardiomyopathy. The percent of patients with sporadic DCM that have a genetic basis is not well characterized. The majority of pathologic mutations 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 genetic mutations 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 mutations in the LMNA, SCN5A, and DES.

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 mutations, 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% to 40% of patients who are referred for genetic testing will have a pathologic mutation identified. Pathologic mutations associated with 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), and alpha-tropomysin (TPM1). These four genes account for approximately 30% of pathologic mutations identified in cohorts of patients with DCM. A high proportion of the identified mutations are rare, or novel, variants, thus creating challenges in assigning the pathogenicity of discovered variants.

Genetic testing can be performed on any of a number of candidate genes individually or collectively. Because of the large number of potential mutations associated with DCM and the infrequent nature of most
Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
Current Effective Date: 03/19/2014

mutations, panel testing is frequently offered. Some examples of genetic panels for DCM that are commercially available are provided in Table 1.

Table 1. Commercially Available Genetic Panels for Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>No. of Genes Tested</th>
<th>Testing Method</th>
</tr>
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<tbody>
<tr>
<td>Ambry Genetics</td>
<td>DCM panel</td>
<td>37</td>
<td>Next-gen sequencing</td>
</tr>
<tr>
<td>GeneDX</td>
<td>DCM sequencing panel</td>
<td>38</td>
<td>Next-gen sequencing</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathies Del/Dup Panel</td>
<td>20</td>
<td>CGH</td>
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<tr>
<td>Transgenomic</td>
<td>DCM panel</td>
<td>13</td>
<td>Sanger sequencing</td>
</tr>
<tr>
<td></td>
<td>Conduction disease-DCM Panel</td>
<td>2</td>
<td>Sanger sequencing</td>
</tr>
<tr>
<td>Partners Healthcare</td>
<td>DCM panel</td>
<td>27</td>
<td>Next-gen sequencing</td>
</tr>
<tr>
<td>Baylor COM</td>
<td>DCM panel</td>
<td>8</td>
<td>Sanger sequencing</td>
</tr>
</tbody>
</table>

DCM: Dilated cardiomyopathy.
Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
Current Effective Date: 03/19/2014

Some individuals with DCM will be found to have more than 1 pathologic DCM mutation. The frequency of multiple mutations is not certain, as is the clinical significance.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
No U.S. FDA-cleared genotyping tests were identified. The available commercial genetic tests for epilepsy are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**
The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

**Analytic Validity**
Commercially available genetic testing for DCM involves a variety of methods such as chip-based oligonucleotide hybridization, direct sequencing of protein-coding portions and flanking regions of targeted exons, and next-generation sequencing. The analytic validity is highest for direct sequencing, approaching 100%. For other methods of genetic testing, the analytic validity may be lower and less precisely defined. For genomic hybridization and next-generation sequencing, the analytic sensitivity is in the range of 95% to 99%.

**Clinical Validity**
There are numerous studies that evaluate the percentage of patients with clinically diagnosed DCM who have pathologic mutations. These studies vary in the genes examined and methods used to detect mutations. The most common type of study describes the presence of 1 type of mutation in probands with DCM or family members of the proband.

There are fewer studies that evaluate cohorts of patients with DCM for the presence of any known DCM mutation. Hershberger et al examined cohort of 313 patients with DCM, 183 with familial DCM and 130 with sporadic DCM. There were a total of 31 unique variants identified in 36 probands (11.5%). The 6 genes evaluated and the frequencies of mutations identified were MYH7 (4.2%), TNNT2 (2.9%), SCN5A (2.6%), TCAP (1.0%), LDB3 (1.0%), and CSRP3 (0.3%). However, only 11 of the 31 probands had variants that were judged to be probably pathologic. The remainder were judged to be possibly pathologic (n=21) or unlikely pathologic (n=4).
Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
Current Effective Date: 03/19/2014

In 2011, Millat et al examined a cohort of 105 unrelated patients with DCM. Sixty-four individuals had familial DCM and 41 had sporadic DCM. All the coding exons and intronic junctions of the MYH7, LMNA, TNNT2, TNNI3, and RBM20 genes were examined by high-resolution melting and direct sequencing. Pathologic mutations were found in 19% (20/105) of individuals. Ten mutations were novel variants and 9 were previously described variants.

In 2012, Lakdawala studied 264 unrelated adult and pediatric individuals with DCM, approximately half of whom had familial disease. Ten genes (MYH7, TNNT2, TNNI3, TPM1, MYBPC3, ACTC, LMNA, PLN, TAZ, LDB3) were analyzed by direct sequence analysis. A total of 40 unique pathologic mutations were identified in 17.4% (46/264) of individuals with DCM. The genes with the most frequent mutations were MYH7 (6.6%), LMNA (5.3%), and TNNT2 (3.7%). Variants of uncertain significance were identified in an additional 10.6% (28/264) of individuals.

Use of next-generation sequencing technology may lead to higher sensitivity for detecting mutations. Herman et al analyzed TTN mutations in 312 individuals with a clinical diagnosis of DCM. This study also included control groups of 231 individuals with hypertrophic cardiomyopathy and 249 individuals without heart disease. Next-generation sequencing techniques were used to identify variants on the TTN gene, and these variants were further characterized by polymerase chain reaction– and dideoxy-sequencing; restriction digestion, and gel electrophoresis; or RNA-sequencing.

Mutations in the TTN gene that were judged to be pathologic were identified in 67/312 (21.5%) individuals with DCM. There were 72 unique mutations identified, 25 nonsense, 23 frameshift, 23 splicing, and 1 large insertion. TTN mutations were found in 3/231 (1%) of patients with hypertrophic cardiomyopathy and 7/249 (3%) of patients without heart disease, which was a significantly lower frequency compared with patients with DCM (p<0.001).

Whole-exome sequencing of 4 genes was used by Hirtle-Lewis et al as part of a strategy to identify and classify genetic variants associated with DCM. The population consisted of 96 patients with idiopathic DCM treated at 1 clinic in Canada. The 4 genes examined were LMNA, TNNT2, TCAP, and PLN, all of which had been previously examined by direct-sequence analysis without any pathologic variants identified. A total of 11 variants were identified, 7 of which were novel variants. Two of the variants were judged to have a high probability of causing disease, 4 were judged to be variants of unknown significance, with the remainder being benign variants.

Section Summary
The clinical validity of genetic testing for DCM is relatively low. The clinical sensitivity is uncertain, but likely to be less than 40%. New mutations continue to be discovered, and next-generation sequencing methods may accelerate gene discovery. The clinical specificity is also uncertain, but variants thought to pathologic have been reported in some patients without cardiomyopathy. The use of next-generation sequencing may decrease clinical specificity if it identifies more variants of uncertain significance.
Genetic Testing for Dilated Cardiomyopathy

Policy #  00409
Original Effective Date:  03/19/2014
Current Effective Date:  03/19/2014

Clinical Utility
The potential clinical utility of genetic testing for DCM includes confirmation of the diagnosis, evaluating whether there is a genetic cause in an individual with idiopathic DCM, and/or evaluating whether a close relative has inherited a disease-causing mutation that is known to be present in the family.

In order to demonstrate clinical utility, the results of genetic testing should be associated with some changes in management that lead to improved outcomes. Changes in management could include initiation of therapy in a patient in whom the diagnosis is confirmed, and/or changes in screening or surveillance for at-risk family members.

Confirming the diagnosis of DCM. Genetic testing could have utility if it was able to confirm the diagnosis of DCM when the diagnosis cannot be made clinically, or if it were used to confirm a diagnosis earlier than would otherwise be possible without genetic testing, and if earlier diagnosis led to management changes that improve outcomes.

The diagnosis of DCM is made on clinical grounds, requiring the presence of left ventricular enlargement and evidence of systolic dysfunction. The presence or absence of a genetic mutation will not alter the clinical diagnosis of DCM. Genetic testing may have an influence on the diagnostic workup for the underlying etiology of DCM. In patients with a likely familial component, genetic testing may improve the efficiency of workup by avoiding other tests for secondary causes of DCM that are likely to be negative. In patients with sporadic forms of DCM, testing for secondary causes will likely still precede genetic testing, so that genetic testing will not influence the diagnostic workup.

Treatment for DCM does not vary according to whether a genetic mutation is present. While there is general agreement that early treatment for DCM is optimal, there are no trials that demonstrate improved outcomes with presymptomatic treatment compared with waiting until the onset of symptoms. If early treatment is based primarily on genetic testing, then the additional concerns of false positive and false negative tests need to be considered.

Predictive testing. In family members of patients with DCM, genetic testing can be used to determine if a known pathologic mutation has been inherited. There are several issues in predictive testing for DCM that create challenges in establishing clinical utility. This first requires confidence that the mutation identified in the proband is causative of DCM. If this is not the case, then genetic testing may provide misleading information. Because of the high number of novel mutations and variants of unknown significance identified in DCM, the confidence that a mutation is causative of the disorder is less than for some other conditions.

The uncertain penetrance and variable clinical expression also needs to be considered in determining the utility of predictive testing. Because of the heterogeneity in clinical expression, it may not be possible to adequately counsel an asymptomatic patient on the likelihood of developing DCM even when an inherited mutation has been identified.
Genetic Testing for Dilated Cardiomyopathy

Policy #  00409
Original Effective Date:  03/19/2014
Current Effective Date:  03/19/2014

Predictive testing may lead to changes in screening and surveillance, particularly for patients who test negative in whom surveillance might be discontinued. However, it is not certain that this approach will lead to improved outcomes. For example, a proband may be identified with a variant that is possibly pathologic. A close family member may test negative for that variant and be falsely reassured that they are not at risk for DCM when they still may harbor another undiscovered mutation.

Section Summary
Clinical utility of genetic testing for DCM has not been established. Genetic testing is not likely to alter the diagnosis of DCM, which is based on clinical factors. For some patients with likely familial disease, the diagnostic workup may be altered, but the extent of change and the impact on outcomes is unclear. Predictive testing may have some role in testing at-risk family members but is currently limited by the low clinical validity of testing, and heterogeneity in penetrance and clinical expression of disease.

Summary
DCM is a disorder of cardiac muscle that leads to progressive left ventricular enlargement, heart failure, and/or cardiac arrhythmias. A subset of DCM is caused by genetic mutations. Genetic forms of DCM are heterogeneous in the types of genetic mutations, clinical expression, and hereditability.

Many genetic mutations on more than 40 different genes have been associated with DCM. This remains an active area of research, and it is likely that many more mutations will be identified in the future. The analytic validity of genetic testing for DCM is expected to be high when testing is performed by direct sequencing or next-generation sequencing. In contrast, the clinical validity is not high. The percent of patients with idiopathic DCM who have a genetic mutation (clinical sensitivity) is relatively low, in the range of 30% to 40%. The clinical specificity of DCM-associated mutations is not known, but DCM-associated mutations in the some genes have been reported in 1% to 3% of patients without DCM.

The clinical utility of genetic testing for DCM is uncertain. For a patient who is diagnosed with idiopathic DCM, the presence of a genetic mutation will not change treatment or prognosis. For an individual at risk due to genetic DCM in the family, genetic testing can identify whether the mutation has been inherited. However, it is uncertain how knowledge of a mutation will improve outcomes for an asymptomatic individual. Early treatment based on a genetic diagnosis is unproven. The uncertain accuracy of predictive testing makes it uncertain whether changes in management will improve outcomes. Because of the low clinical validity and uncertain clinical utility, genetic testing for dilated cardiomyopathy is considered investigational in all situations.

References
Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
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19. 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 2011; 8(8):1308-39.

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Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
Current Effective Date: 03/19/2014

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

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<th>Code Type</th>
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<td>ICD-9 Diagnosis</td>
<td>All relative diagnoses</td>
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<td>ICD-9 Procedure</td>
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**Policy History**

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Current Effective Date: 03/19/2014
03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 03/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and 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. 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.

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