Clinical Policy Title: Genetic testing for hereditary cardiomyopathy

Clinical Policy Number: CCP.1252

Effective Date: October 1, 2016
Initial Review Date: August 17, 2016
Most Recent Review Date: August 1, 2018
Next Review Date: August 2019

Related policies:

CCP.1175 Genetic testing for cytochrome p450 polymorphisms
CCP.1176 Genetic testing for G1691A polymorphisms factor V Leiden
CCP.1037 Genetic testing for long QT syndrome
CCP.1374 Genetic testing for maple syrup urine disease
CCP.1233 Genetic testing for Alzheimer’s disease
CCP.1002 Maternal genetic testing
CCP.1050 Familial polyposis gene testing
CCP.1045 Gene expression profile testing for breast cancer
CCP.1124 Genetic testing for autism spectrum disorders
CCP.1012 Genetic testing for breast and ovarian cancer
CCP.1153 Genetic testing for cystic fibrosis
CCP.1060 Genetic testing for rare diseases
CCP.1121 Genetic testing for prostate cancer prognosis
CCP.1171 Genetic testing in neurology
CCP.1198 Genetic testing in sensorineural hearing loss

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state and federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of genetic testing for hereditary cardiomyopathy susceptibility to be clinically proven and, therefore, medically necessary for
• Molecular confirmation of a clinical diagnosis in symptomatic patients.
• Molecular confirmation of anatomical abnormalities on imaging studies suggestive of hereditary cardiomyopathy.
• Risk assessment of asymptomatic first-degree family members of a proband with cardiomyopathy and/or arrhythmia.
• Differentiation of hereditary cardiomyopathy and/or arrhythmia from acquired (non-genetic) cardiomyopathy and/or arrhythmia.
• Recurrence risk calculation (Hershberger, 2018a; Hershberger, 2018b; Gersh, 2011).

Limitations:

All other uses of genetic testing for hereditary cardiomyopathic syndromes are considered investigational/experimental, and therefore not medically necessary.

Alternative covered services:

• Primary care and specialty care evaluation and diagnosis.
• Laboratory examination.
• Radiologic examination.

Background

Cardiac myocardial enlargement is termed cardiomyopathy. In many cases, cardiomyopathy is the direct result of a disease or specific physiologic disorder (e.g., sarcoidosis, alcoholism). In others it may be a result of genetic mutation of cardiac muscle cells that interfere with normal function, and in general, ventricular function (primarily the left and in some instances the right side of the heart).

The term “hypertrophic cardiomyopathy” is reserved for cardiomyopathy that is unaccounted for by known disease or disorder and is related to a genetic mutation that affects the sarcomere (the fundamental contractile unit of cardiac muscle). It is inherited with variable penetrance; thus, an individual may have the mutation but lack any clinical evidence of the disease. Conversely, if an individual has the signs and symptoms of hypertrophic cardiomyopathy the likelihood the mutated gene will be found on testing is high (Gersh, 2011).

Dilated cardiomyopathy may arise as a primary genetic disorder or as a secondary manifestation of other cardiovascular or systemic conditions (Burke, 2016). It is relatively common in clinical practice, occurring in one in 250 individuals (Hershberger, 2013). Altered myocardial calcium homeostasis is a common feature in genetic and acquired forms of dilated cardiomyopathy and can impact cardiac physiology by causing irregularities in contractile force, signaling pathways, and gene transcription.
Arrhythmic right ventricular dysplasia is a familial disease in around 50 percent of cases and is usually transmitted in an autosomal dominant fashion (Saugner, 2014). It is rare clinically, and characterized pathologically as a progressive fibro-fatty replacement of the right ventricular musculature. The first gene associated with this condition, arrhythmic right ventricular dysplasia 1, coding for a desmosome protein, was discovered in 1994. Hereditary conditions known to cause this restrictive cardiomyopathy include hemochromatosis, glycogen storage diseases, Fabry disease, Gaucher disease, and Hurler syndrome.

For those in whom the genetic mutation is present and expressed in phenotype the clinical consequences can be severe. Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death among young athletes. Hypertrophic cardiomyopathy is also associated with congestive heart failure, malignant cardiac arrhythmias, stroke and need for heart transplantation. Dilated cardiomyopathy is a progressive disorder that most commonly leads to congestive heart failure and premature death. Arrhythmic right ventricular dysplasia predisposes towards malignant arrhythmias originating from the right ventricle and is a known cause of sudden death in young athletes. As a result, early detection of carriers of these genetic variations is desirable in order that prevention, diagnosis, treatment, follow-up and counseling (including pre-natal counseling) of those affected can be accomplished.

Significant complications from hypertrophic cardiomyopathy include the following not mutually exclusive disorders:

1. Sudden cardiac death due to unpredictable tachyarrythmias, most commonly in young (<35 years old) asymptomatic patients, including athletes
2. Heart failure marked by exertional dyspnea (with or without chest pain) that may be progressive to the end stage
3. Atrial fibrillation (paroxysmal or chronic), also linked with heart failure, and elevated risk of systemic thromboembolism and fatal/nonfatal stroke (Gersh, 2011).

Searches

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on May 7, 2018. Searched terms were: "hereditary," "cardiomyopathy (MeSH)" and "hereditary cardiomyopathy."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use
predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A 2018 practice guideline issued by the American College of Medical Genetics and Genomics replaced a 2009 guideline from both the College and the Heart Failure Society of America. The more recent guideline asserted the necessity for genetic evaluation for persons diagnosed with cardiomyopathy, and also includes recommended clinical approaches after secondary findings from cardiomyopathy genes (Hershberger, 2018b). A 2011 guideline from the American College of Cardiology Foundation and American Heart Association recommended that genetic testing for hypertrophic cardiomyopathy be accompanied by genetic counseling from a trained professional, and that in the case of positive results, first-degree relatives be screened for the genetic evidence of the disorder (Gersh, 2011). The European Society of Cardiology also maintains a set of guidelines for diagnosing and managing hereditary cardiomyopathy (Elliott, 2014).

Conclusive medical evidence exists supporting genetic testing for hereditary cardiomyopathy susceptibility is impactful in influencing treatment outcomes for symptomatic patients and those identified with anatomical abnormalities on imaging studies suggestive of hereditary cardiomyopathy. Adjunctive benefits include risk assessment of asymptomatic family members, differentiation of hereditary cardiomyopathy and/or arrhythmia from acquired (non-genetic) cardiomyopathy and/or arrhythmia, and recurrence risk calculation. Notable among sources of this evidence are:

- Among pathogenic variants covering 91 genes in 100 samples implicated in Mendelian diseases, 98.6 percent (91,743,296/93,062,298) of pathogenic variants demonstrated adequate depth for detection in exome sequencing, comparable to panel-based sequencing (LaDuca, 2017).

- A systematic review of 8,097 patients explored the relationship between genotypes and clinical phenotypes in dilated cardiomyopathy. Among other findings, average frequency of mutations was between one and five percent, and the mean age of dilated cardiomyopathy onset was the beginning of the fifth decade for all genes (Kayvanpour, 2017).

Genetic testing has become a key factor in diagnosing cardiovascular genetic disorders to prevent sudden cardiac death in young persons (Shepherd, 2009).

With the expanded availability of next generation sequencing genetic tests, clinicians seeking to test patients with Mendelian diseases must weigh the superior coverage of targeted gene panels with the
greater number of genes included in whole exome sequencing when considering their first-tier testing approach (LaDuca, 2017). Pathogenic variants were represented in 91 genes (n=1533) implicated in hereditary cancer, X-linked intellectual disability, primary ciliary dyskinesia, Marfan syndrome/aortic aneurysms, cardiomyopathies and arrhythmias. When assessing coverage among 100 individual samples for each pathogenic variant (153,300 individual assessments), 99.7 percent (n = 152,798) would likely have been detected.

Women with inherited cardiomyopathy who become pregnant have an elevated heart failure risk. A systematic review of such (asymptomatic) women found most tolerate pregnancy well, but poorly functioning women are at high risk for maternal cardiac complications. Authors endorse genetic counseling and testing to pregnant women after diagnosis of inherited cardiomyopathy (Krul, 2011).

Policy updates:

A total of two guidelines/other and four peer-reviewed references were added to, and three guidelines/other and three peer-reviewed references removed from this policy in July 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>LaDuca (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Next generation sequencing of clinical genetic tests</td>
<td>• With the expanded availability of next generation sequencing-based clinical genetic tests, clinicians seeking to test patients with Mendelian diseases must weigh the superior coverage of targeted gene panels with the greater number of genes included in whole exome sequencing when considering their first-tier testing approach.</td>
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<td></td>
<td>• Corresponding nucleotide positions for 1533 different alterations classified as pathogenic or likely pathogenic identified on targeted next-generation sequencing multi-gene panel tests in our laboratory were interrogated in data from 100 randomly-selected clinical whole exome sequencing samples to quantify the sequence coverage at each position.</td>
</tr>
<tr>
<td></td>
<td>• Pathogenic variants represented 91 genes implicated in hereditary cancer, X-linked intellectual disability, primary ciliary dyskinesia, Marfan syndrome/aortic aneurysms, cardiomyopathies and arrhythmias.</td>
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<tr>
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<td>• When assessing coverage among 100 individual whole exome sequencing samples for each pathogenic variant (153,300 individual assessments), 99.7 percent (n = 152,798) would likely have been detected on whole exome sequencing.</td>
</tr>
<tr>
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<td>• All pathogenic variants had at least some coverage on exome sequencing, with a total of 97.3% (n = 1491) detectable across all 100 individuals.</td>
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<td></td>
<td>• For the remaining 42 pathogenic variants, the number of whole exome sequencing samples with adequate coverage ranged from 35 to 99. Factors such as location in guanine cytosine-rich, repetitive, or homologous regions likely explain why some of these alterations were not detected across all samples.</td>
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<td>• Results from a test validation confirmed that 98.6% (91,743,296/93,062,298) of pathogenic variants demonstrated adequate depth for detection.</td>
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<td>• The authors concluded that exome sequencing may achieve a diagnostic yield similar to panel-based testing for Mendelian diseases.</td>
</tr>
<tr>
<td>Kayvanpour (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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| Genotype-phenotype associations in dilated cardiomyopathy | - A systematic review inclusive of 8097 patients explored the relationship between genotypes and clinical phenotypes in dilated cardiomyopathy.  
- The average frequency of mutations was between 1 and 5%.  
- The mean age of dilated cardiomyopathy onset was the beginning of the fifth decade for all genes.  
- Heart transplant rate was highest in lamin A/C mutation carriers (27%), while RNA binding motif protein 20 mutation carriers were transplanted at a markedly younger age (mean 26.5 years).  
- While 73% of dilated cardiomyopathy patients with lamin A/C mutations showed cardiac conduction diseases, low voltage was the reported electrocardiogram hallmark in phospholamban mutation carriers.  
- The frequency of ventricular arrhythmia in dilated cardiomyopathy patients with lamin A/C (50%) and phospholamban (43%) mutations was significantly higher.  
- The penetrance of dilated cardiomyopathy phenotype in subjects with titin variants increased with age and reached 100% by age 70 years. |
| Ho (2015) Genetic advances in sarcomeric cardiomyopathies: state of the art | Key points:  
- Narrative review of genetic testing for hypertrophic cardiomyopathy and dilated cardiomyopathy.  
- Prenatal diagnosis can be made at the beginning of pregnancy using chorionic villus sampling or amniocentesis. |
| Gersh (2011) American College of Cardiology Foundation/American Heart Association guideline for the diagnosis and treatment of hypertrophic cardiomyopathy | Key points:  
- Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with hypertrophic cardiomyopathy.  
- Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease.  
- Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with hypertrophic cardiomyopathy.  
- Genetic testing for hypertrophic cardiomyopathy and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of hypertrophic cardiomyopathy or when another genetic condition is suspected to be the cause.  
- Testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing hypertrophic cardiomyopathy.  
- The usefulness of genetic testing in the assessment of risk of sudden cardiac death in hypertrophic cardiomyopathy is uncertain and is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.  
- In individuals with pathogenic mutations who do not express the hypertrophic cardiomyopathy phenotype, it is recommended to perform serial electrocardiograph, transthoracic echocardiogram, and clinical assessment at 12 to 18 months in children and adolescents and every five years in adults. |
| Hudecova (2009) Genetic screening of patients with hypertrophic cardiomyopathy -- a new diagnostic strategy for risk stratification | Key points:  
- Clinical symptoms of hypertrophic cardiomyopathy are partly dependent on mutations in affected sarcomere genes.  
- The objective is accurate risk stratification of individuals who carry these genetic defects.  
- The authors concluded that there is also validity in prenatal diagnostic assessment and genetic counseling for individuals at risk for inherited cardiomyopathy. |
Shephard (2009)

Advances in the prevention of sudden cardiac death in the young.

Key points:

- Narrative review noted that implantable cardioversion defibrillator therapy has been the single major advance in the prevention of sudden cardiac death in the young.
- Awareness and family screening of relatives identification of previously unrecognized at-risk individuals.
- Genetic testing is emerging as a key factor in early diagnosis of cardiovascular genetic disorders.

References

Professional society guidelines/other:


Peer-reviewed references:


Burke MA, Chang S, Wakimoto H, et al. Molecular profiling of dilated cardiomyopathy that progresses to


**Centers for Medicare & Medicaid National Coverage Determination:**
No National Coverage Determinations were identified as of the writing of this policy.

Local Coverage Determinations:

No Local Coverage Determinations were identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>81439</td>
<td>Inherited cardiomyopathy genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTN</td>
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<table>
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<tr>
<th>ICD-10 Code</th>
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<td>I42.9</td>
<td>Hereditary cardiomyopathy</td>
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<tr>
<td>Z82.41</td>
<td>Family history of sudden cardiac death</td>
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<tr>
<td>Z86.74</td>
<td>Personal history of sudden cardiac death</td>
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<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>S3866</td>
<td>Genetic analysis for a specific mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM in the family</td>
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