Clinical Policy Title: Genetic testing for hereditary cardiomyopathy

Coverage policy

Keystone First 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 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.

Limitations:

All other uses of genetic testing for hereditary cardiomyopathic syndromes are not medically necessary.

Note: The following CPT/HCPCS code is not listed in the Pennsylvania Medicaid fee schedule:

S3866 - Genetic analysis for a specific mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM in the family

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 interferes 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 (HCM)” 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 a fairly common condition in clinical practice, occurring in an estimated one in 500 individuals (Maron 2006). 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 HCM the likelihood the mutated gene will be found on testing is 60 percent (Richard 2003).

Dilated cardiomyopathy (DC) may arise as a primary genetic disorder or as a secondary manifestation of other cardiovascular or systemic conditions (Burke 2016). It, too, 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 DC and can impact cardiac physiology by causing irregularities in contractile force, signaling pathways, and gene transcription.

Arrhythmic right ventricular dysplasia (ARVD) is a familial disease in around 50 percent of cases and is usually transmitted in an autosomal dominant fashion (Nava 1998). 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, ARVD-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. HCM is the most common cause of sudden cardiac death (SCD) among young athletes. HCM is also associated with congestive heart failure, malignant cardiac arrhythmias, stroke and need for heart transplantation. DC is a progressive disorder that most commonly leads to congestive heart failure (CHF) and premature death. ARVD 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.

**Searches**

Keystone First 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 (CMS).

We conducted searches on June 6, 2016. 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**

Elliot (2014) wrote on behalf of the European Society of Cardiology a set of guidelines for diagnosis and management of HCM:

- Genetic counseling is recommended in all patients when HCM cannot be explained solely by a non-genetic cause.
- Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives.
- When a definite causative genetic mutation is identified in a patient, his or her relatives should be genetically tested, and then clinically evaluated if they are found to carry the same mutation.
The phenomenon of age-related penetrance means that a normal clinical evaluation does not exclude the possibility of disease development in the future; first-degree relatives should therefore be offered repeat assessment. Clinical and genetic testing of children should be guided by the best interests of each child. Clinical data suggests that clinically important events in asymptomatic children are rare before puberty; thus, it is reasonable in these children to defer clinical and/or genetic screening until the age of 10 years.

Gersh (2011) wrote on behalf of the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines that evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM, and that patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient. The ACCF/AHA group also stated that screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM, and genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM 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 HCM. The usefulness of genetic testing in the assessment of risk of SCD in HCM 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 HCM phenotype, it is recommended to perform serial electrocardiogram (ECG), transthoracic echocardiogram (TTE), and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient’s age and change in clinical status.

The Heart Failure Society of America’s practice guideline on "Genetic evaluation of cardiomyopathy" (Hershberger 2009) stated that genetic testing is primarily indicated for risk assessment in at-risk relatives who have little or no clinical evidence of cardiovascular disease. Genetic testing for HCM should be considered for the one most clearly affected person in a family to facilitate family screening and management. Specific genes available for testing for HCM include MYH7, MYBPC3, TNNT2, TNN13, TPM1, ACTC, MYL2, and MYL3. Genetic cause can be identified in 35 to 50 percent overall; up to 60 percent when the family history is positive.

Hudcova (2009) noted that the clinical symptoms of HCM are partly dependent on mutations in affected sarcomere genes. The authors posited that the objective of genetic testing for these conditions is in the 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.

Ho (2015) followed with a narrative review of genetic testing for HCM and DC, noting that prenatal genetic diagnosis can be performed at the beginning of pregnancy using chorionic villus sampling or amniocentesis.

Shephard (2009) in a narrative review offered that genetic heart disorders are an important cause of SCD in the young. The authors noted that the introduction of implantable cardioverter-defibrillator (ICD) therapy has been the single major advance in the prevention of SCD in the young, and offers an avenue of management of potential value to those at risk to heritable cardiomyopathy. In addition, the awareness that most causes of SCD in the young are inherited means family screening of relatives of
young SCD victims allows identification of previously unrecognized at-risk individuals, and facilitates prevention of SCD in relatives. The role of genetic testing is emerging as a key factor in early diagnosis of underlying cardiovascular genetic disorders.

Summary of clinical evidence:

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<th>Citation</th>
<th>Content</th>
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<tr>
<td>Elliott (2014)</td>
<td><strong>Key points:</strong></td>
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| Guidelines on diagnosis and management of hypertrophic cardiomyopathy | - European Society of Cardiology guidelines for HCM:  
- Genetic counseling is recommended in all patients when HCM cannot be explained solely by a non-genetic cause.  
- Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives.  
- When a definite causative genetic mutation is identified in a patient, his or her relatives should be genetically tested, and then clinically evaluated if they are found to carry the same mutation.  
- The phenomenon of age-related penetrance means that a normal clinical evaluation does not exclude the possibility of disease development in the future; first-degree relatives should therefore be offered repeat assessment.  
- Clinical and genetic testing of children should be guided by the best interests of each child. Clinical data suggests that clinically important events in asymptomatic children are rare before puberty; thus, it is reasonable in these children to defer clinical and/or genetic screening until the age of 10 years. |
| Gersh (2011)                            | **Key points:**                                                                                                                       |
| ACCF/AHA Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy | - Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM.  
- 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 HCM.  
- Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM 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 HCM.  
- The usefulness of genetic testing in the assessment of risk of SCD in HCM 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 HCM phenotype, it is recommended to perform serial ECG, TTE, and clinical assessment at 12 to 18 months in children and adolescents and every 5 years in adults. |
| Hershberger (2009)                      | **Key points:**                                                                                                                       |
| Genetic evaluation of cardiomyopathy--a Heart Failure Society of America practice guideline. | - The Heart Failure Society of America’s guideline on genetic evaluation of cardiomyopathy  
- Genetic testing is indicated for risk assessment in at-risk relatives who have little or no clinical evidence of cardiovascular disease.  
- Genetic testing for HCM should be considered for the one most clearly affected person in a family to facilitate family screening and management. |
| Hudecova (2009)                         | **Key points:**                                                                                                                       |
| Genetic screening of                    | - Clinical symptoms of HCM are partly dependent on mutations in affected sarcomere genes. |
|                                         |                                                                         |
patients with hypertrophic cardiomyopathy -- a new diagnostic strategy for risk stratification

- 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.

Ho (2015)
Genetic advances in sarcomeric cardiomyopathies: state of the art

Key points:
- Narrative review of genetic testing for HCM and DC.
- Prenatal diagnosis can be made at the beginning of pregnancy using chorionic villus sampling or amniocentesis.

Shephard (2009)
Advances in the prevention of sudden cardiac death in the young.

Key points:
- Narrative review noted that ICD) therapy has been the single major advance in the prevention of SCD 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.

Glossary

Genetic testing (also known as gene expression assay and gene expression profiling) — A type of test that is used to determine the presence or absence of a specific gene or set of genes to help diagnose a disease, screen for specific health conditions and for other purposes.

Hypertrophic cardiomyopathy (HCM) — A constrictive, sometimes congenital and inherited defect of the heart muscle, which compromises normal cardiac function (i.e., the left ventricle) and is associated with considerable morbidity and mortality.

Mutation — A change in sequence that may occur spontaneously or as a result of carcinogens and co-factors introduced to human DNA. These mutations may in some cases be hereditary and affect multiple members of a family.

Sudden cardiac death (SCD) — An unanticipated death from a heart-related condition, including cardiomyopathy.

References

Professional society guidelines/other:


Peer-reviewed references:


**Clinical Trials:**

Searched clinicaltrials.gov on June 9, 2016 using term “hereditary cardiomyopathy” | Open Studies. 8 studies found, 2 relevant.


**CMS National Coverage Determination (NCDs):**

No NCDs were identified.

**Local Coverage Determinations (LCDs):**

No LCDs were identified.

**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.

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