Title: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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</table>
| Individuals:  
  • Who are asymptomatic with risk for hypertrophic cardiomyopathy because of a positive family history | Interventions of interest are:  
  • Testing for specific hypertrophic cardiomyopathy–related variant identified in affected family member(s) | Comparators of interest are:  
  • Clinical management without genetic testing | Relevant outcomes include:  
  • Overall survival  
  • Test accuracy  
  • Test validity  
  • Changes in reproductive decision making  
  • Symptoms  
  • Morbid events |
| Individuals:  
  • Who are asymptomatic with risk for hypertrophic cardiomyopathy because of a positive family history | Interventions of interest are:  
  • Nonspecific testing for hypertrophic cardiomyopathy–related variant | Comparators of interest are:  
  • Clinical management without genetic testing | Relevant outcomes include:  
  • Overall survival  
  • Test accuracy  
  • Test validity  
  • Changes in reproductive decision making  
  • Symptoms  
  • Morbid events |
DESCRIPTION

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition that is caused by a variant in one or more of the cardiac sarcomere genes. HCM is associated with numerous cardiac abnormalities, the most serious of which is sudden cardiac death (SCD). Genetic testing for HCM-associated variants is currently available through a number of commercial laboratories.

OBJECTIVE

The objective of this policy is to determine whether genetic testing improves health outcomes in individuals who are asymptomatic but at risk for hypertrophic cardiomyopathy because of a positive family history.

BACKGROUND

Familial Hypertrophic Cardiomyopathy

Familial HCM is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately 1 in 500 adults (0.2%).\(^1\) It is the most common cause of sudden cardiac death (SCD) in adults younger than 35 years of age and is probably also the most common cause of death in young athletes.\(^2\) The overall death rate for patients with HCM is estimated to be 1% per year in the adult population.\(^3,4\)

The genetic basis for HCM is a defect in the cardiac sarcomere, which is the basic contractile unit of cardiac myocytes composed of a number of different protein structures.\(^5\) Nearly 1400 individual variants in at least 18 different genes have been identified to date.\(^6-9\) Approximately 90% of pathogenic variants are missense (ie, 1 amino acid is replaced for another), and the strongest evidence for pathogenicity is available for 11 genes coding for thick filament proteins (MYH7, MYL2, MYL3), thin filament proteins (TNNT2, TNNI3, TNNC1, TPM1, ACTC), intermediate filament proteins (MYBPC3), and the Z-disc adjoining the sarcomere (ACTN2, MYOZ2). Variants in myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) are the most common and account for roughly 80% of sarcomeric HCM. These genetic defects are inherited in an autosomal dominant pattern with rare exceptions.\(^5\) In patients with clinically documented HCM, genetic abnormalities can be identified in approximately 60%.\(^7,9\) Most patients with clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants.\(^10\)

Diagnosis

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy (LVH), measured by echocardiography or magnetic resonance imaging (MRI), in the absence of other known causative factors such as valvular disease, long-standing hypertension, or other myocardial disease.\(^7\) In addition to primary cardiac disorders, there are systemic diseases that can lead to LVH and thus “mimic” HCM. These include infiltrative diseases such as amyloidosis, glycogen storage diseases such as Fabry disease and Pompe disease, and neuromuscular disorders such as Noonan syndrome and
Friederich ataxia.9 These disorders need to be excluded before a diagnosis of familial HCM is made.

HCM is a very heterogeneous disorder. Manifestations range from subclinical, asymptomatic disease to severe life-threatening disease. Wide phenotypic variability exists among individuals, even when an identical variant is present, including among affected family members.2 This variability in clinical expression may be related to environmental factors and modifier genes.11 A large percentage of patients with HCM, perhaps the majority of all HCM patients, are asymptomatic or have minimal symptoms.10,11 These patients do not require treatment and are not generally at high risk for SCD. A subset of patients has severe disease that causes a major impact on quality of life and life expectancy. Severe disease can lead to disabling symptoms, as well as complications of HCM, including heart failure and malignant ventricular arrhythmias. Symptoms and presentation may include SCD due to unpredictable ventricular tachyarrhythmias, heart failure, or atrial fibrillation, or some combination.12 Management of patients with HCM involves treating cardiac comorbidities, avoiding therapies that may worsen obstructive symptoms, treating obstructive symptoms with β-blockers, calcium channel blockers, and (if symptoms persist) invasive therapy with surgical myectomy or alcohol ablation, optimizing treatment for heart failure, if present, and SCD risk stratification. ICD implantation may be indicated if there is a family history of SCD.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for screening in clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals ages 12 to 18 years and every 3 to 5 years for adults.11 Additional screening is recommended for any change in symptoms that might indicate the development of HCM.11

Genetic Testing
Genetic testing has been proposed as a component of screening at-risk individuals to determine predisposition to HCM among those patients at risk. Patients at risk for HCM are defined as individuals who have a close relative with established HCM. Results of genetic testing may influence management of at-risk individuals, which may in turn lead to improved outcomes. Furthermore, results of genetic testing may have implications for decision making in the areas of reproduction, employment, and leisure activities.

Commercial testing has been available since May 2003, and numerous companies currently offer genetic testing for HCM.6,13-16 Testing is performed either as comprehensive testing or targeted gene testing. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes that are most commonly associated with genetic variants for HCM and evaluates whether any potentially pathogenic variants are present. Some available panels include testing for
multisystem storage diseases that may include cardiac hypertrophy, such as Fabry
disease (GLA), familial transthyretin amyloidosis (TTR), X-linked Danon disease (LAMP2).

Other panels include testing for genes related to HCM but also those associated with
other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel
(ApolloGen, Irvine, CA) is an next-generation sequencing (NGS) panel of 44 genes
associated with HCM, dilated cardiomyopathy, restrictive cardiomyopathy,
arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic
ventricular tachycardia, left ventricular noncompaction syndrome, Danon syndrome,
Fabry disease, Barth syndrome, and transthyretin amyloidosis.

For a patient with a known variant in the family, targeted testing is performed. Targeted
variant testing evaluates for the presence or absence of a single variant known to exist in
a close relative.

It can be difficult to determine the pathogenicity of genetic variants associated with HCM.
Some studies have reported that assignment of pathogenicity has a relatively high error
rate and that classification changes over time. With NGS and whole-exome
sequencing techniques, the sensitivity of identifying variants on the specified genes has
increased substantially. At the same time, the number of variants of uncertain
significance is also increased with NGS. In addition, the percentage of individuals who
have more than 1 variant that is thought to be pathogenic is increasing. A 2013 study
reported that 9.5% (19/200) patients from China with HCM had multiple pathogenic
variants and that the number of variants correlated with severity of disease.

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 Act (CLIA). Sequencing tests for
hypertrophic cardiomyopathy (HCM) 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 (FDA) has chosen not to require any
regulatory review of this test.

There are no assay kits approved by FDA for genetic testing for HCM.
POLICY

A. Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered **medically necessary** for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene variant present in that affected relative (see Policy Guidelines).

B. Genetic testing for predisposition to HCM is considered **not medically necessary** for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathologic variants.

C. Genetic testing for predisposition to HCM is considered **experimental / investigational** for all other patient populations, including, but not limited to, individuals who have a first-degree relative with clinical HCM, but in whom genetic testing is unavailable.

Policy Guidelines

1. Due to the complexity of genetic testing for HCM and the potential for misinterpretation of results, the decision to test and the interpretation of test results should be performed by, or in consultation with, an expert in the area of medical genetics and/or hypertrophic cardiomyopathy.

2. To inform and direct genetic testing for at-risk individuals, genetic testing should initially be performed in at least 1 close relative with definite HCM (index case), if possible.

3. Because there are varying degrees of penetrance for different HCM variants, consideration for testing of second- or third-degree relatives may be appropriate in certain circumstances. Some judgment should be allowed for these decisions, for example, in the case of a small family pedigree. Consultation with an expert in medical genetics and/or the genetics of HCM, in conjunction with a detailed pedigree analysis, is appropriate when testing of second- or third- degree relatives is considered.

4. 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.

5. Genetics Nomenclature Update: Human Genome Variation Society (HGVS) 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. HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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

<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.

**RATIONALE**

This policy has been updated regularly with searches of the MEDLINE database. The initial review was based primarily on a 2009 TEC Assessment. The most recent update with literature review covered the period through January 25, 2017.

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, 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). Following is a summary of the key literature.

The TEC Assessment reviewed the evidence on the accuracy of genetic testing in identifying patients who will subsequently develop hypertrophic cardiomyopathy (HCM) and identified 7 studies meeting inclusion criteria.21-27

**Testing for a Specific HCM-Related Variant**

**Clinical Context and Test Purpose**
The purpose of targeted genetic testing in patients who are asymptomatic but at risk of HCM is to inform management decisions. Genetic testing for HCM may potentially play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

The question addressed in this evidence review is whether testing an asymptomatic individual for a family variant known to be associated with HCM improves outcomes by obviating the need for routine surveillance if the result is negative.

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is asymptomatic individuals with a close relative who has HCM and a known pathogenic variant.

**Interventions**
Targeted genetic testing on the variant(s) identified in the relative with HCM.

**Comparators**
The comparator of interest is standard clinical management without genetic testing such that decisions related to surveillance and medical therapy are based on guidelines for patients with a relative with HCM.

**Outcomes**
If the test has a high negative predictive value, the main beneficial outcome would be to safely reduce or eliminate the need for routine clinical surveillance for signs and symptoms of HCM. Potential harmful outcomes are those resulting from a false test result. False-positive results can lead to initiation of unnecessary treatment and adverse effects from that treatment. False-negative results could lead to delay in diagnosis and treatment.

**Timing**
Appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of onset of HCM from genetic causes. Changes in outcomes due to increased surveillance or early initiation of treatment in asymptomatic patients would take many years to become evident.

**Setting**
Family members of individuals diagnosed with HCM may be referred to a secondary or tertiary care setting for clinical screening and genetic testing. Genetic counseling is important for providing
family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Analytic Validity**
For predispositional genetic testing, the analytic validity (ability to detect or exclude a specific variant; in this case, the specific variant of interest is a variant identified in another family member) were evaluated. The analytic validity is more relevant when there is a known variant in the family, whereas the clinical validity is more relevant for individuals without a known variant in the family.

The analytic sensitivity (probability that a test will detect a specific variant that is present) of sequence analysis for detecting variants that cause HCM is likely to be very high based on what is known about the types of variants that cause HCM and the limited empirical data provided by manufacturers and detailed descriptions of the testing methodology. There are fewer data available on the analytic specificity (probability that a test will be negative when a specific variant is absent) of HCM testing. The available information on specificity, mainly from series of patients without a personal or family history of HCM, suggests that false-positive results for known pathologic variants are uncommon.\(^{23,27}\)

Therefore, for a patient with a known variant in the family, the high analytic validity means that targeted genetic testing for a familial variant has high predictive value for both a positive (variant detected) and a negative (variant not detected) test result. A negative test indicates that the individual is free of the variant, while a positive test indicates that the patient has the variant and is at risk for developing HCM in the future.

**Clinical Validity**
A positive genetic test result does not indicate that the individual has clinical HCM. The other important component to clinical validity in this context is penetrance, or the probability that an individual with a pathogenic variant will eventually develop the condition of concern. There is reduced penetrance in HCM (ie, not everyone with a deleterious variant will develop manifestations of HCM).\(^{28}\) In addition, penetrance varies among different variants and may even vary among different families with an identical pathogenic variant.\(^{29}\) As a result, it is not possible to estimate accurately the penetrance for any given variant in a specific family. Multiple pathogenic variants are found in 1% to 10% of patients with HCM and are associated with more severe disease and a worse prognosis.\(^{7,19}\) For these patients, targeted analysis may miss variants other than the one tested for. Some experts recommend comprehensive testing of all individuals for this reason; however, it is not known whether the presence of multiple pathogenic variants influences management decisions such that health outcomes might be improved.

**Clinical Utility**
**Predictive Testing: Detection in At-Risk Individuals**
There are benefits to predisposition genetic testing for at-risk individuals when there is a known disease-associated variant in the family. Inheritance of the predisposition to HCM can be ruled out with near certainty when the genetic test is negative (variant not detected) in this circumstance. A positive test result (variant detected) is less useful. It confirms the presence of a pathogenic variant and an inherited predisposition to HCM but does not establish the presence of the disease. It is possible that surveillance for HCM may be increased after a positive test, but the changes in
management are not standardized, and it is also possible that surveillance will be essentially the same following a positive test.

Michels et al (2009) attempted to risk-stratify asymptomatic patients with a positive genetic test for HCM.30 They reported cardiac evaluation outcomes and risk stratification for sudden cardiac death (SCD) in 76 asymptomatic HCM variant carriers identified from 32 families. Between 2007 and 2008, 76 asymptomatic family members of 32 probands with HCM and known variants were found to have variants in 1 or more genes. HCM was diagnosed in 31 (41%) asymptomatic family members. The authors attempted to risk-stratify patients for SCD, and found that none of the screened carriers was symptomatic, had a history of syncope, or had severe hypertrophy (≥30 mm). Four carriers were found to have an abnormal blood pressure response during exercise, which is associated with worse prognosis; of those, 3 were diagnosed with HCM. Three carriers were found to have nonsustained ventricular tachycardia, which is also associated with worse prognosis in HCM; of those, 2 were diagnosed with HCM. The study did not have sufficient follow-up to determine whether these risk factors were associated with differences in SCD rates over the long term.

At present, the management of patients with HCM is not dependent on the identification of a specific variant or any positive variant testing results. However, there is active investigation into treatments that may slow disease progression before the development of overt echocardiographic signs of HCM.31,32

**Carrier Testing: Variant Detection for Reproductive Decision Making**

Knowledge of the results of genetic testing may aid in decision making on such issues as reproduction by informing discussion on the susceptibility to develop future disease. Direct evidence on the impact of genetic information on this type of decision making is lacking, and the effect of such decisions on health outcomes is uncertain.

Additionally, rudimentary disease prevention based on assisted reproduction using preimplantation genetic diagnosis (PGD) is possible. PGD uses in vitro fertilization with a single cell removed from early-stage embryos and tested for the familial variant. Only those embryos without the identified HCM variant are used to initiate pregnancy. Disease-modifying studies are in development using animal models of HCM. In rodent models, sarcomere variants have been implicated in early abnormal intracellular calcium handling far in advance of left ventricular hypertrophy (LVH). Treatment of this calcium handling by use of diltiazem appeared to attenuate the development of LVH when started in early life. The feasibility of this strategy in humans has been assessed in a pilot randomized controlled trial that compared diltiazem to placebo in known sarcomere variant carriers who have yet to develop LVH.32

**Section Summary: Testing for a Specific HCM-Related Variant**

The available evidence on testing for variants related to HCM indicates a high analytic sensitivity and specificity. This suggests that, in cases where there is interest in identifying a specific variant (ie, when there is a known variant in an affected family member), testing can rule in or rule out the presence of a variant with high certainty. On the other hand, variability in clinical penetrance means that a positive genetic test does not rule in clinical HCM, although it makes HCM more likely. The available evidence has not demonstrated that specific genetic testing results are associated with a HCM-related phenotype or disease penetrance. Use of genetic testing for HCM has the greatest utility in asymptomatic family members of patients with HCM who have a known
genetic variant. Given the high sensitivity for known variants, the absence of a variant in the asymptomatic relatives should rule out the presence of familial HCM and allow reduction in surveillance for complications. Detection of variants in asymptomatic carriers may aid reproductive decision making, although direct evidence is limited on the impact of genetic information in this setting.

**Nonspecific Testing for a HCM-Related Variant**

**Clinical Context and Test Purpose**
The purpose of nonspecific genetic testing in patients who are asymptomatic but at risk of HCM is to inform management decisions. Genetic testing for HCM could play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic individuals at risk of developing HCM?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals who are asymptomatic with a close relative who has HCM and an unknown pathogenic variant.

**Interventions**
Nontargeted genetic testing.

**Comparators**
The comparator of interest is standard clinical management without genetic testing such that decisions on surveillance and medical therapy are based on guidelines for patients with a relative with HCM.

**Outcomes**
The general outcomes of interest are overall survival, test accuracy and validity, changes in reproductive decision making, symptoms, and morbid events.

The potential beneficial outcome of primary interest would be reduction in surveillance for the development of HCM. Maintenance of functioning and quality of life are also important.

Potential harmful outcomes are those resulting from a false result. False-positive test results can lead to initiation of unnecessary treatment and adverse effects from that treatment. False-negative test results could lead to delay in diagnosis and treatment.

**Timing**
Appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of HCM onset from genetic causes. Changes in outcomes due to increased surveillance or early initiation of treatment in asymptomatic patients would take many years to become evident.
Setting
Family members of individuals diagnosed with HCM may be referred to a secondary or tertiary care setting for clinical screening and genetic testing. Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
There is some published evidence on the analytic validity of next-generation sequencing panels for genes associated with cardiomyopathies, including HCM. For example, one 17-gene panel was reported to have a maximum 96.7% sensitivity for single-nucleotide variants, with positive predictive values above 95%, compared with Sanger sequencing. The rate of false-positive results is likely to be higher for classification of previously unknown variants.

Clinical Validity
Clinical validity for nonspecific testing is the ability to detect any pathogenic variant in a patient with HCM and to exclude a variant in a patient without HCM. The clinical validity of genetic testing for HCM is considerably lower than the analytic validity. Evidence on clinical sensitivity (probability that a person with HCM, or who will get HCM, will have a positive genetic test result), consists of several case series of patients with established HCM. To date, the published variant detection rate ranges from 33% to 67%. The less-than-perfect variant detection rate is due in part to the published studies having investigated some, but not all, of the known genes that underlie HCM, and investigators in these studies using variant scanning methods such as single-strand conformation polymorphism or denaturing gradient gel electrophoresis that will miss certain deleterious variants. Another reason for the less-than-perfect variant detection rate is that other, as yet unidentified, genes may be responsible for HCM. Finally, there may be unknown, nongenetic factors that mimic HCM. Variant detection rates will likely increase over time with recognition of new variants.

Clinical Utility
If a familial variant is not known and an at-risk individual undergoes testing, a positive result (variant detected) would confirm an inherited predisposition to HCM and an increased risk for clinical manifestations in the future. However, a negative result (no variant detected) could not exclude the possibility that a variant was inherited. In this case, risk assessment and surveillance for HCM would depend on the family history and other personal risk factors. Thus, in this situation, testing has limited utility in decision making. Moreover, if a familial variant is not known, comprehensive variant analysis would be the method of choice, and in addition to a positive or negative result, there is the possibility of detecting a variant of uncertain significance—a variant for which the association with clinical disease is not known.

Section Summary: Nonspecific Testing for a HCM-Related Variant
Given the wide genetic variation in HCM and the likelihood that not all causative variants have been identified, there is imperfect clinical sensitivity. Because of the imperfect clinical sensitivity, a negative test is not sufficient to rule out HCM in patients without a known variant in the family.

Because of the suboptimal clinical sensitivity relating to less-than-perfect variant detection, the best genetic testing strategy for predisposition testing for HCM begins with comprehensive testing (eg, sequence analysis) of a DNA sample from an affected family member. Comprehensive variant analysis in an index patient is important because it informs and directs the subsequent testing of
at-risk relatives. If the same variant is identified in an at-risk relative, then it confirms the inheritance of the predisposition to HCM and the person is at risk for developing the manifestations of the disease. However, if the familial variant is not identified in an at-risk relative, then this confirms that the variant has not been inherited, and there is then a very low likelihood (probably similar to or less than the population risk) that the individual will develop signs or symptoms of HCM. Therefore, clinical surveillance for signs of the disorder can be discontinued, and the patient can be reassured that his or her risk of developing the disease is no greater than that of the general population.

**SUMMARY OF EVIDENCE**

For individuals who are asymptomatic with risk for hypertrophic cardiomyopathy (HCM) because of a positive family history who receive testing for a specific HCM-related variant identified in affected family member(s), the evidence includes studies reporting on the analytic and clinical validity of testing. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, symptoms, and morbid events. For individuals at risk for HCM (first-degree relatives), genetic testing is most useful when there is a known disease-associated variant in the family. In this situation, genetic testing will establish the presence or absence of the same variant in a close relative with a high degree of certainty. Absence of this variant will establish that the individual has not inherited the familial predisposition to HCM and thus has a similar risk of developing HCM as the general population. Such patients will no longer need ongoing surveillance for the presence of clinical signs of HCM. Although no direct evidence comparing outcomes for at-risk individuals managed with and without genetic testing was identified, there is a strong chain of evidence that management changes can improve outcomes with genetic testing when there is a known familial variant. 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 risk for HCM because of a positive family history who receive nonspecific testing for a HCM-related variant, the evidence includes studies reporting on the analytic and clinical validity of testing. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, symptoms, and morbid events. Given the wide genetic variation in HCM and the likelihood that not all causative variants have been identified, there is imperfect clinical sensitivity. Therefore, a negative test is not sufficient to rule out a disease-associated variant in patients without a known family variant. For at-risk individuals without a known variant in the family, there is no clear relation between testing and improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Clinical input was solicited in January 2011 on general agreement with the policy. This was followed up by a second round of focused clinical vetting in October 2011 to address specific questions raised after the first round of vetting. The initial vetting indicated uniform agreement with the medically necessary indication for individuals with a first-degree relative who has a
known pathologic mutation. This vetting also asked whether testing should be restricted to first-degree relatives. For this question, there was a mixed response, with 2 reviewers indicating that they agree with testing only first-degree relatives, two reviewers indicating that testing should be offered to non-first-degree relatives, and 1 reviewer who was unsure.

The second round of clinical vetting focused on the changes in management that could result from genetic testing. Reviewers were uniform in responding that a positive test will result in heightened surveillance. All but 1 reviewer indicated that a negative test will eliminate the need for future surveillance in all cases. There was general agreement that the surveillance schedule used in clinical practice was that proposed by Maron et al (2003).^{10}

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**European Society of Cardiology**

In 2014, the European Society of Cardiology issued guidelines on the diagnosis and management of HCM, which included the following recommendations related to genetic testing (see Table 1).^{36}

**Table 1. European Society of Cardiology Guidelines on Diagnosis and Management of HCM**

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendations</th>
<th>LOE</th>
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<tbody>
<tr>
<td>I</td>
<td>Genetic counselling is recommended for all patients with HCM when their disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Cascade genetic screening, after pre-test counselling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband</td>
<td>C</td>
</tr>
<tr>
<td>IIa</td>
<td>Genetic counselling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Genetic testing in patients with a borderline diagnosis of HCM should be performed only after detailed assessment by specialist teams</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives</td>
<td>C</td>
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<tr>
<td></td>
<td>First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2–5 years (or 6–12 monthly if non-diagnostic abnormalities are present)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing—following pre-test family counselling—when they are aged 10 or more years and this should be carried out in accordance with international guidelines for genetic testing in children</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>In first-degree child relatives aged 10 or more years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1–2 years between 10 and 20 years of age, and then every 2–5 years thereafter</td>
<td>C</td>
</tr>
<tr>
<td>IIb</td>
<td>If requested by the parent(s) or legal representative(s), clinical assessment with ECG and echocardiography may precede or be substituted for genetic evaluation after counselling by experienced physicians and when it is agreed to be in the best interests of the child</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical or genetic</td>
<td>C</td>
</tr>
</tbody>
</table>
American College of Cardiology Foundation and the American Heart Association
The American College of Cardiology Foundation and the American Heart Association issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy in 2011.12 Table 2 lists the recommendations on genetic testing.

Table 2. ACCF and AHA Joint Guidelines on Diagnosis and Treatment of HCM

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendations</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>B</td>
</tr>
<tr>
<td>IIa</td>
<td>Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM</td>
<td>B</td>
</tr>
<tr>
<td>IIb</td>
<td>The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM</td>
<td>B</td>
</tr>
</tbody>
</table>

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; HCM: hypertrophic cardiomyopathy; LOE: level of evidence; SCD: sudden cardiac death.

Heart Rhythm Society and the European Heart Rhythm Association
The Heart Rhythm Society and the European Heart Rhythm Association published recommendations for genetic testing for cardiac channelopathies and cardiomyopathies in 2011.37 For hypertrophic cardiomyopathy, the following recommendations (both class I) were made:

- Comprehensive or targeted ... HCM genetic testing is recommended for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient’s clinical history, family history, and electrocardiographic/echocardiographic phenotype
- Mutation-specific testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 3.
## Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01915615</td>
<td>HCMR - Novel Markers of Prognosis in Hypertrophic Cardiomyopathy</td>
<td>2750</td>
<td>Nov 2018</td>
</tr>
<tr>
<td>NCT00156429</td>
<td>Genetic Predictors of Outcome in HCM Patients</td>
<td>540</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT: national clinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

<table>
<thead>
<tr>
<th>CPT/HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81407</td>
<td>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt;50 exons, sequence analysis of multiple genes on one platform)</td>
</tr>
<tr>
<td>81439</td>
<td>Inherited cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTN</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>S3865</td>
<td>Comprehensive gene sequence analysis for hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>S3866</td>
<td>Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family</td>
</tr>
</tbody>
</table>

- Effective in 2013, there are CPT codes that can be used to report this testing: 81403, 81405, 81406, 81407, 81479.

- There are specific HCPCS “S” codes for this testing: S3865 and S3866

### ICD-9 Diagnoses

- 425.11 Hypertrophic obstructive cardiomyopathy
- 425.4 Other primary cardiomyopathies
- V17.41 Family history of sudden cardiac death [SCD]
- V17.49 Family history of other cardiovascular diseases
V82.719  Screening for genetic disease carrier status
V82.79   Other genetic screening

ICD-10 Diagnoses *(Effective October 1, 2015)*

- I42.1  Obstructive hypertrophic cardiomyopathy
- I42.2  Other hypertrophic cardiomyopathy
- I42.8  Other cardiomyopathies
- Z82.41  Family history of sudden cardiac death
- Z82.49  Family history of ischemic heart disease and other diseases of the circulatory system

**REVISIONS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>03-26-2012</td>
<td>Policy added to the bcbsks.com web site.</td>
</tr>
<tr>
<td>04-08-2013</td>
<td>Posted to the web site on 03-08-2013 to give 30 days notice to professional and institutional providers.</td>
</tr>
<tr>
<td></td>
<td>Description section updated</td>
</tr>
<tr>
<td></td>
<td>Rationale section updated</td>
</tr>
<tr>
<td></td>
<td>In Coding section: Added CPT codes: 81405, 81406, 81407, 81479 (effective 01-01-2013) Updated coding notations. Added Diagnosis codes 425.11, 425.4, V17.41, V17.49, V82.719, V82.79 which had been erroneously left off the policy. Removed the phrase &quot;Experimental / Investigational on all diagnoses related to this medical policy.&quot; which had been incorrectly placed on the policy.</td>
</tr>
<tr>
<td></td>
<td>References updated</td>
</tr>
<tr>
<td>12-31-2013</td>
<td>In Coding section: Nomenclature updated on CPT codes: 81405, 81406 ICD-10 Diagnoses added.</td>
</tr>
<tr>
<td>03-31-2015</td>
<td>Description section updated</td>
</tr>
<tr>
<td></td>
<td>Rational section updated</td>
</tr>
<tr>
<td></td>
<td>In Coding section:</td>
</tr>
<tr>
<td></td>
<td>Updated bulleted coding directions</td>
</tr>
<tr>
<td></td>
<td>References updated</td>
</tr>
<tr>
<td>01-01-2016</td>
<td>In Coding section:</td>
</tr>
<tr>
<td></td>
<td>Updated CPT code 81405 nomenclature</td>
</tr>
<tr>
<td></td>
<td>Updated References section.</td>
</tr>
<tr>
<td>02-17-2016</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>In Policy section:</td>
</tr>
<tr>
<td></td>
<td>In Item B, added &quot;with established HCM&quot; to read &quot;Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathologic mutations.</td>
</tr>
<tr>
<td></td>
<td>In Policy Guidelines, added Item 4 on genetic counseling.</td>
</tr>
<tr>
<td></td>
<td>Updated Rationale section.</td>
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<tr>
<td></td>
<td>In Coding section:</td>
</tr>
<tr>
<td></td>
<td>Added CPT code 81403.</td>
</tr>
<tr>
<td></td>
<td>Updated References section.</td>
</tr>
<tr>
<td></td>
<td>Added Appendix section.</td>
</tr>
<tr>
<td>01-01-2017</td>
<td>In Coding section:</td>
</tr>
<tr>
<td></td>
<td>Added CPT code 81439 <em>(New code, effective January 1, 2017).</em></td>
</tr>
<tr>
<td>04-12-2017</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>In Policy section:</td>
</tr>
</tbody>
</table>
|            | In Item A, added "variant" and removed "mutation" and "section" to read, "Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered
medically necessary for individuals who are at risk for development of HCM, defined
as having a first-degree relative with established HCM, when there is a known
pathogenic gene variant present in that affected relative (see Policy Guidelines)."

- In Item B, added "variants" and removed "mutation" to read, "Genetic testing for
  predisposition to HCM is considered not medically necessary for patients with a
  family history of HCM in which a first-degree relative with established HCM has tested
  negative for pathologic variants."
- In Policy Guidelines, added Item 5.

Updated Rationale section.
Updated References section.
Updated Appendix section.

REFERENCES
   2008;16(4):172-180. PMID 18562807
2. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the
   PMID 18382207
6. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical
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8. Ghosh N, Haddad H. Recent progress in the genetics of cardiomyopathy and its role in the clinical
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    PMID 15183628
11. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of
    Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the
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    European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. Nov 5
    2003;42(9):1687-1713. PMID 14607462
    hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American
    PMID 22068434
    ventricular tachycardia in patients with nonischemic cardiomyopathy: acute results and its effect on

37. 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

Other References

APPENDIX

Appendix Table 1. Categories of Genetic Testing Addressed In This Policy

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual's germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td>X</td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: mutations</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>