Policy Statement

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered medically necessary when both of the following criteria are met:

- Individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM (See Policy Guidelines section)
- Known pathogenic gene variant present in that affected relative (See Policy Guidelines section)

Genetic testing for predisposition to hypertrophic cardiomyopathy (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 pathogenic variants.

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered 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

First degree relatives are defined as a blood relative with whom the individual shares approximately 50% of his/her genes, including parents, full-siblings, and children on both maternal and paternal sides.

Due to the complexity of genetic testing for hypertrophic cardiomyopathy (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 HCM.

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

Recommendations indicate that, when possible, genetic testing for hypertrophic cardiomyopathy be performed in an affected family member so that testing in unaffected, at-risk family members can focus on the variant found in the affected family member. This testing is intended to document whether a known pathologic variant is present in the family and to optimize the predictive value of predisposition testing for at-risk relatives. However, coverage for testing of the affected index case depends on contract benefit language when there is no conclusive evidence of clinical benefit to the index case from testing.

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 (e.g., 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.

Genetics Nomenclature Update

The 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 (see Table...
PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 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.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

There are CPT codes that can be used to report this testing.

The following CPT code is a genomic sequencing procedure code for panels:
- **81439**: Hereditary cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)

Hypertrophic Cardiomyopathy (HCM) (Known Mutation) (when specified for hypertrophic cardiomyopathy):
- **81403**: Molecular Pathology Procedure Level 4
  - PLN (phospholamban) (e.g., dilated cardiomyopathy, hypertrophic cardiomyopathy), full gene sequence

Hypertrophic Cardiomyopathy (HCM) (full gene sequencing):
- **81405**: Molecular Pathology Procedure Level 6
• ACTC1 (actin, alpha, cardiac muscle 1) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• MYL2 (myosin, light chain 2, regulatory, cardiac, slow) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• MYL3 (myosin, light chain 3, alkali, ventricular, skeletal, slow) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• TNNC1 (troponin C type 1 [slow]) (e.g., hypertrophic cardiomyopathy or dilated cardiomyopathy), full gene sequence
• TNNI3 (troponin I, type 3 [cardiac]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• TPM1 (tropomyosin 1 [alpha]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• 81406: Molecular Pathology Procedure Level 7
  • TNNT2 (troponin T, type 2 [cardiac]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• 81407: Molecular Pathology Procedure Level 8
  • MYBPC3 (myosin binding protein C, cardiac) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
  • MYH7 (myosin, heavy chain 7, cardiac muscle, beta) (e.g., familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence

• 81479: Unlisted molecular pathology procedure

The following code would be used to report ACTN2 and MYOZ2 testing:

• S3865: Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
• S3866: Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

**Description**

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition caused by a disease-associated 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. Genetic testing for HCM-associated variants is available through a number of commercial laboratories.

**Related Policies**

• N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Sequencing tests for HCM are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

No assay kits have been approved by the Food and Drug Administration for genetic testing for HCM.

Rationale

Background

Familial Hypertrophic Cardiomyopathy

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

The genetic basis for HCM is a defect in the cardiac sarcomere, which is the basic contractile unit of cardiac myocytes and is composed of different protein structures. Around 1400 disease-associated variants in at least 18 different genes have been identified. About 90% of pathogenic variants are missense (i.e., 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 Zdisc 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. In patients with clinically documented HCM, genetic abnormalities can be identified in approximately 60%-90%. Most patients with the clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants.

Diagnosis and Management

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy, measured by echocardiography or magnetic resonance imaging, in the absence of other known causative factors such as valvular disease, long-standing hypertension, or another myocardial disease. In addition to primary cardiac disorders, there are systemic diseases that can lead to left ventricular hypertrophy and thus mimic HCM. They include infiltrative diseases such as amyloidosis, glycogen storage diseases (e.g., Fabry disease, Pompe disease), and neuromuscular disorders (e.g., Noonan syndrome, Friedreich ataxia). 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. This variability in clinical expression may be related to environmental factors and modifier genes. A large percentage of patients with HCM, perhaps the majority, are asymptomatic or have minimal symptoms. 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.11

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. Implantable cardioverter defibrillator 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 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.10 Additional screening is recommended for any change in symptoms that might indicate the development of HCM.10

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 the 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. However, the likelihood of obtaining a positive genetic test in the proband is only about 50% because all genes causing HCM have not yet been identified or are absent from testing panels. Failure to identify the causative variant in the proband is an indeterminate result that provides no useful information and precludes predictive testing in 33% to 67% of cases.

Commercial testing has been available since 2003, and numerous companies offer genetic testing for HCM.5,12,13,14,15 Testing is performed either as a comprehensive or targeted gene test. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes 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), and X-linked Danon disease (LAMP2).

Other panels include testing for genes related to HCM and those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen) is a next-generation sequencing 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.16

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.17,18 With next-generation sequencing 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 next-generation sequencing. Also, the percentage of individuals who have more than one 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.19.

**Literature Review**

This review was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2009).20 That TEC Assessment reviewed the evidence on the accuracy of genetic testing in identifying patients who would subsequently develop hypertrophic cardiomyopathy (HCM) and identified seven studies meeting inclusion criteria.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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

**Clinical Context and Test Purpose**

The purpose of targeted genetic testing of patients who are asymptomatic but at-risk of HCM is to inform management decisions. Genetic testing for HCM would 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 variant known to be associated with HCM identified in a family member improves net health outcomes.

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

**Patients**

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

**Interventions**

The test being considered is targeted genetic testing for 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.

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

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

When a patient tests positive for a specific HCM-related variant, the clinical validity of a test to detect that specific variant in an asymptomatic first-degree relative relies on two factors: the analytic validity of the test itself and the penetrance (the probability that an individual with an identified pathogenic variant already has HCM or will develop HCM in the near future). 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 a higher risk for developing HCM in the future.

Multiple studies have been published on the phenotypic penetrance of HCM, which ranges from 50% to 100% and is briefly summarized below.

- Variants in the MYBPC3 gene are the most common cause (14% to 26%) of HCM. Approximately 40% of adults under the age of 50 with MYBPC3 variants do not have cardiac hypertrophy, and disease penetrance may remain incomplete through the age of 60.21
- Variants in the MYH7 gene are found in 13% to 25% of patients with HCM and are associated with a high penetrance of disease, younger age at diagnosis, and more severe hypertrophy. However, there is substantial clinical heterogeneity in the phenotypic expression of HCM in such patients. Survival in those with HCM due to variants in MYH7 gene varies considerably despite nearly complete disease penetrance and significant hypertrophy.22,23,24
- Variants in the cTnI gene are found in 2% to 7% of patients of HCM with a disease penetrance of approximately 50%.22,25,26

Studies relating to clinical validity are summarized below.

Observational Studies
Several observational studies evaluated genetic testing of asymptomatic relatives of probands and measured the number of relatives who received HCM diagnoses after cardiac evaluations. Table 1 summarizes the results of these studies.

Michels et al (2009) conducted cardiac evaluations on 76 asymptomatic family members with known HCM variants identified through genetic testing of 32 probands.27 Of the 76 asymptomatic family members, HCM was diagnosed in 31 (41%) cases based on results from cardiac evaluation, electrocardiography, Doppler echocardiography, exercise testing, and 24 hour Holter monitoring.
Cardoso et al (2017) reported on the outcomes of 17 first-degree relatives of 3 probands. Of the 17 tested, 14 child relatives were variant carriers (70% median age, 8 years) of whom 7 (50%) were diagnosed with HCM at initial assessment. After 3.5 years of follow-up, 2 of the phenotype negative genotype positive children developed HCM at 10 and 15 years of age (28% penetrance rate).

Van Velzen et al (2018) conducted a retrospective analysis of asymptomatic relatives of 209 patients with HCM. Genetic testing and counseling had been offered to all probands. In the cohort, 196 (94%) of the probands underwent genetic testing. Among the patients who were identified as variant-positive (149 of 196), 626 (80%) of the asymptomatic relatives underwent genetic testing. Cardiac screening was performed on the 264 relatives who were variant-positive and on the 157 relatives who did not undergo genetic testing (n=421). Based on the cardiac evaluation, HCM was diagnosed in 126 (30%) of the relatives who were variant-positive and in 98 (37%) of the relatives who did not undergo genetic testing. After a median follow-up of nine years of relatives with HCM at baseline, all-cause mortality was 0.7% and cardiac mortality was 0.3%. After a median of 7 to 8 years of follow-up of relatives without HCM at baseline, all-cause mortality was 0.1% and HCM developed in 29 (16%).

### Table 1. Observational Studies of Asymptomatic Patients with Known HCM Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Number with HCM Diagnosis after Variant Detection and Cardiac Evaluation (%)</th>
<th>Followup, years</th>
<th>Number with HCM Diagnosis after Followup (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michels (2009)²⁷</td>
<td>Case series</td>
<td>Asymptomatic relatives who tested positive for HCM variant (n=76)</td>
<td>31 (41)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Cardoso (2017)²⁸</td>
<td>Case series</td>
<td>Asymptomatic child relatives who tested positive for HCM variant (n=14)</td>
<td>7 (50)</td>
<td>3.5</td>
<td>2 (28)</td>
</tr>
<tr>
<td>van Velzen (2018)²⁹</td>
<td>Retrospective cohort</td>
<td>Asymptomatic relatives who tested positive for HCM variant (n=264)</td>
<td>98 (37)</td>
<td>7</td>
<td>29 (16)</td>
</tr>
</tbody>
</table>

HCM: hypertrophic cardiomyopathy; NA: not applicable

Additional observational studies evaluated clinical outcomes of patients with HCM and known variants.

Ko et al (2018) conducted a survey of patients with HCM with and without variants and assessed first-degree family members for development of HCM-related adverse events. Patients were recruited from a registry of patients with HCM who had genetic testing. A total of 120 patients completed the survey: 56 had pathogenic variants; 49 had no variants; 11 had variants of undetermined significance; and 4 had benign variants. A positive genetic test was associated with younger age at diagnosis, greater wall thickness, and absence of hypertension. Among patients with either a positive genetic test or family history, 34 of 203 first degree relatives (17%) reported an HCM diagnosis. Among patients without genetic variants and no prior family history, 2 of 64 first degree relatives who were screened reported an HCM diagnosis.

Lopes et al (2018) conducted genotype-phenotype analyses of probands and relatives (n=424) in the Portuguese registry of HCM. The mean time of follow-up after diagnosis was 5.7 years (median of three years). Patients with a known variant were significantly more likely to have a family history of HCM, a family history of sudden cardiac death, and no history of hypertension. Patients with a known variant were significantly more likely to have an American Heart Association/American College of Cardiology risk factor for sudden cardiac death compared
with patients without a known variant. Genotype-positive status was associated with sudden cardiac death but was not associated with overall mortality or cardiovascular mortality.

**Systematic Review**

Sedaghat-Hamedani et al (2017) conducted a systematic review and meta-analysis of studies assessing the genotype-phenotype associations in patients with HCM and variants in the following genes: MYBPC3, MYH7, TNNT2, and TNNI3.\textsuperscript{32} The literature search included studies from 1998 through 2015 and identified 51 studies with a total of 7675 patients with HCM. The authors state that a quality assessment of the studies was performed but do not provide details on this assessment. Several studies reported heart transplantation rates among patients with HCM and either MYBPC3 or MYH7 variants. Patients with the MYH7 variant underwent significantly more heart transplantations compared with patients with the MYBPC3 variant (p=0.006). An analysis was also conducted comparing sudden cardiac deaths among patients with and without MYBPC3, MYH7, and TNNT2 variants. Sudden cardiac death occurred more frequently among patients with one of the variants compared with patients with no variants (p<0.001).

Table 2 provides a summary of variant frequency and mean age of disease onset.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Number Studies, variant frequency</th>
<th>Number patients</th>
<th>Variant Frequency, % (95% CI)</th>
<th>Number Studies, disease onset</th>
<th>Mean age (95% CI) at disease onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYBPC3</td>
<td>31</td>
<td>6132</td>
<td>20 (17 to 23)</td>
<td>19</td>
<td>39 (37 to 41)</td>
</tr>
<tr>
<td>MYH7</td>
<td>31</td>
<td>5688</td>
<td>14 (12 to 15)</td>
<td>21</td>
<td>35 (29 to 41)</td>
</tr>
<tr>
<td>TNNT2</td>
<td>23</td>
<td>5267</td>
<td>2 (2 to 3)</td>
<td>7</td>
<td>39 (34 to 43)</td>
</tr>
<tr>
<td>TNNI3</td>
<td>19</td>
<td>4289</td>
<td>2 (1 to 2)</td>
<td>2</td>
<td>44 (25 to 64)</td>
</tr>
</tbody>
</table>

CI: confidence interval; HCM: hypertrophic cardiomyopathy.

**Section Summary: Clinically Valid**

The available evidence suggests that, in cases where there is interest in identifying a specific variant (i.e., when there is a known variant in an affected family member), testing can rule in or rule out the presence of that 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. Several studies that followed relatives who tested positive for an HCM variant, reported that HCM occurred at a rate of 40% to 60%.

**Clinically Useful**

A test is clinically useful if use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

No studies comparing outcomes for at-risk asymptomatic individuals managed with and without genetic testing were identified. Some studies have reported on cross-sectional or long-term follow-up of outcomes in single cohorts. These studies also showed that multiple pathogenic variants may occur in 1% to 10% of patients with HCM and are associated with more severe disease and a worse prognosis.\textsuperscript{6,19} For these patients, the targeted analysis might miss variants other than the one tested. For this reason, some experts recommend comprehensive testing of all individuals; however, it is not known whether the presence of multiple pathogenic variants influences management decisions such that health outcomes might be improved.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There is a range of benefits to genetic testing for at-risk individuals when there is a known disease-associated variant in the family.
A positive test would imply that the individual has inherited the variant from the proband and can be placed under HCM surveillance using cardiac imaging to detect the development of the phenotype and adoption of therapy and lifestyle adaptations. However, it is important to underscore that because of variable penetrance, an individual with a positive test may not develop clinical disease in the future and, as such, all adopted interventions may not have an impact.

A negative test would imply that the individual has not inherited the variant from the proband and clinical surveillance for HCM can be discontinued, and the patient can be reassured that his or her risk of developing the disease may be no greater than that of the general population. However, it is important to underscore that because of suboptimal clinical sensitivity relating to the less-than-perfect variant detection, an individual with a negative test could still develop clinical disease due to, as yet, unidentified or de novo variants.

Section Summary: Testing for a Specific HCM-Related Variant

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 a reduction in surveillance for complications. Detection of variants in asymptomatic carriers may lead to the adoption of HCM surveillance with cardiac imaging to detect the development of the phenotype and possible institution of therapy and lifestyle adaptations. Further, they may help in 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 of 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 are individuals who are asymptomatic with a close relative who has HCM and an unknown pathogenic variant.

Interventions

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

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

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

A test is clinically useful if use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Evidence of clinical sensitivity (the probability that a person with clinical 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 rates range 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, 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 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 improve over time with recognition of new variants.

Ingles et al (2018) identified 24 gene panels for HCM or left ventricular hypertrophy and evaluated the clinical validity evidence on the genes included in those panels, using the National Institutes of Health Clinical Genome Resource framework. All panels including key sarcomere genes. Results of the evaluation found that of the 33 genes appearing on HCM panels, 8 (24%) can be classified as “definitive”, 3 (9%) are “moderate”, 16 (49%) are “limited”, and 6 (18%) have “no evidence”. The authors assert that reporting genes that have limited or no evidence causes potential harm to patients who may experience anxiety over results and may undergo unnecessary surveillance or treatment.

Given the wide genetic variation in HCM and the likelihood that not all causative variants have been identified or characterized, 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. On the other hand, if a test detects a variant of uncertain significance, it means there is a variant that could be disease-causing or benign. Inconclusive results may cause more harm than benefit to the patient and relatives. Additional information is necessary to understand the clinical significance.
Clinically Useful
A test is clinically useful if use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. No published studies comparing outcomes for at-risk asymptomatic individuals managed with and without genetic testing were identified.

No studies comparing outcomes for at-risk asymptomatic individuals, managed with nonspecific genetic testing for an HCM-related variant, were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. The evidence on clinical validity is insufficient to demonstrate test performance, and therefore no inferences can be made.

A chain of evidence cannot be constructed to support the use of nonspecific genetic testing of at-risk asymptomatic individuals for an HCM-related variant.

Section Summary: Nonspecific Testing for a HCM-Related Variant
If the variant identified in the tested family member is of uncertain significance, testing unaffected at-risk family members for the variant is not helpful, because this information will not aid in interpretation of the variant and will not reliably modify the a priori risk to that relative of developing HCM. If no variant is identified in the tested family member, no further genetic testing can be pursued to clarify the genetic status of at-risk family members. No direct evidence comparing outcomes for at-risk individuals managed with and without genetic testing was identified, and a strong chain of evidence that management changes improve outcomes with genetic testing cannot be made. Thus, in these situations, testing has limited utility in decision making.

Summary of Evidence
For individuals who are asymptomatic with risk for 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 clinical validity of testing. The 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. Presence of the variant indicates that the relative should undergo a cardiac evaluation upon receiving the variant-positive results. If an HCM diagnosis is not made at that time, the patient should be monitored for development of symptoms. 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. 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 an HCM-related variant, the evidence includes studies reporting
on the clinical validity of testing. The 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.

Supplemental Information

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.

In response to requests from Blue Cross Blue Shield Association, input was received in 2011. Input was solicited in January 2011 on general agreement with the policy and again 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 pathogenic variant. This vetting also asked whether testing should be restricted to first-degree relatives. To this question, there was a mixed response, with two reviewers indicating that they agreed with testing only first-degree relatives, two reviewers indicating that testing should be offered to non-first-degree relatives, and one reviewer who was unsure.

The second round of vetting focused on changes in management that could result from genetic testing. Reviewers were uniform that a positive test would result in heightened surveillance. All but one reviewer indicated that a negative test would 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

The European Society of Cardiology (2014) issued guidelines on the diagnosis and management of hypertrophic cardiomyopathy (HCM), which included the following recommendations related to genetic testing (see Table3).38.

Table3. Guidelines on Diagnosis and Management of HCM

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic counseling 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>I</td>
<td>B</td>
</tr>
<tr>
<td>Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM when it enables cascade genetic screening of their relatives</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<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>I</td>
<td>B</td>
</tr>
<tr>
<td>Cascade genetic screening, after pre-test counseling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<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>I</td>
<td>C</td>
</tr>
<tr>
<td>Genetic counseling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
Recommendations | COR | LOE
--- | --- | ---
Genetic testing in patients with a borderline diagnosis of HCM should be performed only after detailed assessment by specialist teams | IIa | C
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 | IIa | C
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 | IIa | B
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) | IIa | C
The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing following pre-test family counseling when they are aged 10 or more years, and this should be carried out in accordance with international guidelines for genetic testing in children | IIa | C
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 | IIa | C
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 counseling by experienced physicians and when it is agreed to be in the best interests of the child | IIb | C
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 testing of first-degree child relatives before the age of 10 years may be considered | IIb | C
In definite mutation carriers who have no evidence of disease expression, sports activity may be allowed after taking into account the underlying mutation and the type of sports activity, and the results of regular and repeated cardiac examinations | IIb | C

COR: class of recommendation; ECG: electrocardiography; HCM: hypertrophic cardiomyopathy; LOE: level of evidence.

American College of Cardiology Foundation and American Heart Association
The ACC Foundation and the AHA (2011) issued joint guidelines on the diagnosis and treatment of HCM. Table 4 lists the recommendations on genetic testing.

Table 4. Joint Guidelines on Diagnosis and Treatment of HCM

| Recommendations | COR | LOE |
--- | --- | ---
Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM | I | B
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 | I | B
Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM | I | B
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 | I | B
Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM | IIa | B
The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain | IIb | B
Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation | III | B
Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM | III | B

COR: class of recommendation; HCM: hypertrophic cardiomyopathy; LOE: level of evidence; SCD: sudden cardiac death.
The ACC and AHA (2015) issued a joint scientific statement on the eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities. Fifteen Task Forces were assigned to review the scientific evidence for various cardiovascular diseases and with expert consensus, develop recommendations for athletic participation. Table 5 outlines the recommendations related to HCM.

Table 5. ACC/AHA Recommendations for Participation in Sports

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation in competitive athletics for asymptomatic, genotype-positive HCM patients without evidence of LV hypertrophy by 2-dimensional echocardiography and CMR is reasonable, particularly in absence of a family history of HCM-related sudden death.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Athletes with a probable or unequivocal clinical expression and diagnosis of HCM (disease phenotype of LV hypertrophy) should not participate in most competitive sports, with the exception of class IA sports (low intensity).</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

CMR: cardiovascular magnetic resonance imaging; COR: class of recommendation; HCM: hypertrophic cardiomyopathy; LOE: level of evidence; LV: left ventricular; ACC: American College of Cardiology; AHA: American Heart Association.

Heart Rhythm Society and the European Heart Rhythm Association

The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations on genetic testing for cardiac channelopathies and cardiomyopathies. For HCM, 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

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. 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>Apr 2022</td>
</tr>
<tr>
<td>NCT00156429</td>
<td>Genetic Predictors of Outcome in HCM Patients</td>
<td>540</td>
<td>May 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References

38. Maron, BB, Zipes, DD, Kovacs, RR. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Preamble, Principles, and General Considerations: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation, 2015 Dec 2;132(22). PMID 26621642

41. 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


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Tests required
  - Purpose of testing
  - Family history of hypertrophic cardiomyopathy (HCM) including:
    - Family relationship (if applicable)
    - Genetic mutation analysis results in that relative (if applicable)

**Post Service**

- Results/reports of tests performed

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81403</td>
<td>Molecular Pathology Procedure Level 4</td>
</tr>
<tr>
<td></td>
<td>81405</td>
<td>Molecular Pathology Procedure Level 6</td>
</tr>
<tr>
<td></td>
<td>81406</td>
<td>Molecular Pathology Procedure Level 7</td>
</tr>
<tr>
<td></td>
<td>81407</td>
<td>Molecular Pathology Procedure Level 8</td>
</tr>
<tr>
<td></td>
<td>81439</td>
<td>Hereditary cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>G0452</td>
<td>Molecular pathology procedure; physician interpretation and report</td>
</tr>
</tbody>
</table>
### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.