Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Genetic Testing for Inherited Hypertrophic Cardiomyopathy

Description/Background

FAMILIAL HYPERTROPHIC CARDIOMYOPATHY

Familial hypertrophic cardiomyopathy (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 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]

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.[4] Around 1400 disease-associated variants in at least 18 different genes have been identified.[5-8] 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 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.[4] In patients with clinically documented hypertrophic cardiomyopathy, genetic abnormalities can be identified in approximately 60%.[6,9] 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.[9]

Diagnosis and Management

The clinical diagnosis of hypertrophic cardiomyopathy depends on the presence of left ventricular hypertrophy, measured by echocardiography or magnetic resonance imaging (MRI), in the absence of other known causative factors such as valvular disease, long-standing hypertension, or another myocardial disease.[6] In addition to primary cardiac disorders, there are systemic diseases that can lead to left ventricular hypertrophy and thus mimic hypertrophic cardiomyopathy. 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).[9] These disorders need to be excluded before a diagnosis of familial HCM is made.

Hypertrophic cardiomyopathy is a very heterogenous 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.[10] A large percentage of patients with hypertrophic cardiomyopathy, perhaps the majority, are asymptomatic or have minimal symptoms.[9,10] These patients do not require treatment and are not generally at high risk for sudden cardiac death. 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 hypertrophic cardiomyopathy, including congestive heart failure (CHF) and malignant ventricular arrhythmias. Symptoms and presentation may include sudden cardiac death due to unpredictable ventricular tachyarrhythmias, heart failure, or atrial fibrillation, or some combination.[11]

Management of patients with hypertrophic cardiomyopathy 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 sudden cardiac death risk stratification. Implantable cardioverter-defibrillator implantation may be indicated if there is a family history of sudden cardiac death.

Diagnostic screening of first-degree relatives and other family members is an important component of hypertrophic cardiomyopathy 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 aged 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 hypertrophic cardiomyopathy.[10]

Genetic Testing

Genetic testing has been proposed as a component of screening at-risk individuals to determine predisposition to hypertrophic cardiomyopathy among those patients at risk. Patients at risk for hypertrophic cardiomyopathy are defined as individuals who have a close relative with established hypertrophic cardiomyopathy. 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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy.[5,12] Testing is performed either as a comprehensive or targeted gene test. Comprehensive testing, which is done for an individual without a known genetic mutation in the family, analyzes the genes that are most commonly associated with genetic variants for HCM and evaluates whether any potentially pathogenic mutations 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 that are related to hypertrophic cardiomyopathy and those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen, Irvine, CA) is a next-generation sequencing panel of 44 genes that are associated with HCM, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, left ventricular non-compaction syndrome, Danon syndrome, Fabry disease, Barth syndrome, and transthyretin amyloidosis.[13]

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 determining 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.[14,15] With next generation 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 unknown significance is also increased with next generation sequencing. Also, the percent of individuals who have more than 1 mutation that is thought to be pathogenic is increasing. A study in 2013 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 has chosen not to require any regulatory review of this test.

No assay kits have been approved by the U.S. Food and Drug Administration (FDA) for genetic testing for HCM.

Medical Policy Statement

The safety and effectiveness of genetic testing for inherited hypertrophic cardiomyopathy have been established. It may be considered a useful diagnostic and prognostic option for patients meeting patient selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Genetic testing for hypertrophic cardiomyopathy is appropriate for:

- Individuals who display clinical features, or who are pre-symptomatic but are at direct risk of inheriting the mutation in question when:
  - The results of the test will directly impact the diagnostic and treatment options being recommended for the patient, *and*

  - After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies a definitive diagnosis remains uncertain.
- Individuals who are pre-symptomatic and do not meet the clinical features of HCM, but who have:
  - A close relative (i.e., a first- or second- degree relative) with a *known* HCM mutation, or
  - A close relative diagnosed (i.e., a first- or second- degree relative) with HCM by clinical means whose genetic status is unknown.

In addition to the above inclusions,

- The genetic testing should be ordered by a specialist in cardiology or genetics
- Genetic testing must be done in conjunction with genetic counseling. The counselor evaluates medical problems or risks present in a family, analyzes and explains inheritance patterns of any disorders found, provides information about management and treatment of these disorders and discusses available options with the family or individual.

Exclusions:

- Genetic screening for HCM in the general population is excluded because such screening is considered not medically necessary or of unproven benefit.
- Patients not meeting the listed patient selection guidelines.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

S3865 S3866 81405 81406 81407 81479 81439

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

This review was informed by a TEC Assessment (2009).[17] That TEC Assessment reviewed the evidence on the accuracy of genetic testing in identifying patients who would subsequently develop hypertrophic cardiomyopathy (HCM) and identified 7 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 in 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: 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 **PICO** was used to select literature to inform this review.

Populations

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

Interventions

The test being considered is targeted genetic testing on the variant(s) identified in the relative with HCM.

Family members of individuals diagnosed with hypertrophic cardiomyopathy 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.

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.

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 hypertrophic cardiomyopathy 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.

Review of Evidence

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 2 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 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.[18]
- 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.[19-21]
- Variants in the *TNNI3* gene are found in 2% to 7% of patients of HCM with a disease penetrance of approximately 50%.[19,22,23]
- Variants in the *TNNT2, ACTC1, MYL2, MYL3*, and *TPM1* genes encode 1 of the myocardial sarcomeric proteins and are found in ≤4% of patients with HCM with definitive evidence for their pathogenicity.[6]

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 hypertrophic cardiomyopathy variants identified through genetic testing of 32 probands.[24] 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).[25]

van Velzen et al (2018) conducted a retrospective analysis of asymptomatic relatives of 209 patients with HCM.[26] 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. Results from testing of the relatives found 356 variant-negative and 264 variant-positive relatives. 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 9 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%).

Lorenzini et al (2020) evaluated the incidence of new hypertrophic cardiomyopathy diagnoses in sarcomere protein mutation carriers in a retrospective analysis.27 A total of 583 pathogenic/likely pathogenic variant carriers from 307 families were evaluated, with 267 (45.8%) diagnosed with hypertrophic cardiomyopathy at the initial evaluation and thereby excluded from the remainder of the study. An additional 31 subjects underwent a screening visit and were also excluded. This left a final study cohort of 285 subjects (median age: 14.2 years; 49.5% male). The frequency of causal genes was: MYBPC3 (43.2%), MYH7 (24.2%), TNNI3 (13.7%), TNNT2 (11.9%), TPM1 (3.2%), MYL2 (2.1%), ACTC1 (0.4%), and multiple mutations (1.4%). At a median follow-up of 8 years, 86 (30.2%) subjects developed hypertrophic cardiomyopathy and the estimated penetrance at 15 years of follow-up was 46%.

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

Study	Design	Population	Number w/HCM Diagnosis after Variant Detection and Cardiac Evaluation (%)	Follow-Up, Years	Number w/HCM Diagnosis after Follow-up (%)
Michels (2009)[27]	Case series	Asymptomatic relatives who tested positive for HCM variant (n=76)	31 (41)	0	NA
Cardoso (2017)[28]	Case series	Asymptomatic child relatives who tested positive for HCM variant (n=14)	7 (50)	3.5	2 (28)
van Velzen (2018)[29]	Retrospective cohort	Asymptomatic relatives who tested positive for HCM variant (n=264)	98 (37)	7	29 (16)
Lorenzini et al (2020)[27]	Retrospective cohort	Asymptomatic relatives who tested positive for sarcomere protein gene mutations (n=583)	267 (45.8)	8	86 (30.2)

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.[28] 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; 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 a 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.[29] The mean time of follow-up after diagnosis was 5.7 years

(median of 3 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*.[30] 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 (SCDs) among patients with and without *MYBPC3, MYH7,* and *TNNT2* variants. Sudden cardiac death occurred more frequently among patients with 1 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 2. results from Meta-Analysis of Studies Assessing Genetic Variants in Patients with HCM

Gene	Number Studies, Variant Frequency	Number Patients	Variant Frequency, % (95% CI)	Number Studies, Disease Onset	Mean Age (95% CI) at Disease Onset
MYBPC3	31	6132	20 (17 to 23)	19	39 (37 to 41)
MYH7	31	5688	14 (12 to 15)	21	35 (29 to 41)
TNNT2	23	5267	2 (2 to 3)	7	39 (34 to 43)
TNNI3	19	4289	2 (1 to 2)	2	44 (25 to 64)

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.[6,16] For these patients, the targeted analysis might miss variants

other than for 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. Furthermore, misinterpretation of uninformative genetic test results may be high in the hypertrophic cardiomyopathy community.[31]

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 AN 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 **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is 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.

Family members of individuals diagnosed with hypertrophic cardiomyopathy 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.

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 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.

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.

Review of Evidence

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 effectively therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Caser Series
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%,[19,22,31-35] 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.[36] All panels included 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.

Observational Studies

Data from patients diagnosed with HCM in the Sarcomeric Human Cardiomyopathy Registry (SHaRe) (n=4591; 12% with affected relatives; 35% with family history of HCM) indicates that for patients harboring 1 or more sarcomeric pathogenic/likely pathogenic variants, median age at diagnosis was 13.6 years younger than in those with no pathogenic variants (median [37.5 years; interquartile range, 23.6 to 49.8 years] vs. [51.1 years; interquartile range, 38.3 to 61.8 years]; p<0.001).[37] Furthermore, patients with pathogenic/likely pathogenic sarcomere mutations had a 2-fold greater risk for adverse outcomes compared with patients without these mutations and a higher rate of HCM family history (58% vs. 25%; p<0.001).

Maurizi et al (2018) assessed long-term outcomes of pediatric-onset HCM and age-specific risk factors for lethal arrhythmic events.[38] Of 1644 patients with HCM at 2 national referral centers for cardiomyopathies in Italy, 100 (6.1%) were aged 1 to 16 years at diagnosis. Forty-two of the 100 patients were symptomatic (42%) according to New York Heart Association classification >1 or Ross score >2. The yield of sarcomere gene testing was 55 of 70 patients (79%). During a median follow-up period of 9.2 years, 24 of 100 patients (24.0%) experienced cardiac events (1.9% per year), which included 19 lethal arrhythmic events and 5 heart failure-related events. Risk of lethal arrhythmic events was associated with symptoms at onset (hazard ratio 8.2; 95% CI, 1.5 to 68.4; p=0.02). A trend toward an association between lethal arrhythmic event and Troponin I or Troponin T gene mutations was also detected (hazard ratio 4.1; 95% CI, 0.9 to 36.5; p=0.06) but did not reach statistical significance.

Robyns et al (2019) conducted genotype-phenotype analyses of HCM patients to construct a score to predict the genetic yield and improve counseling.[39] Unrelated patients with HCM (n=378) underwent genetic testing for a panel of genes including at minimum MYBPC3, MYH7, and *TNNT2*. Multivariate logistic regression was utilized to identify clinical and electrocardiogram variables that predicted a positive genetic test. In total, 141 patients carried a mutation (global yield 37%), 181 were variant-negative, and 56 carried a variant of uncertain significance. *MYBPC3* variants accounted for 21.6% of the genetic yield. Age at diagnosis <45 years, familial HCM, familial sudden death, arrhythmic syncope, maximal wall thickness ≥20 mm, asymmetrical hypertrophy and the absence of negative T waves on lateral electrocardiogram were significant predictors of a positive genetic test. *MYBPC3* mutation carriers more frequently suffered sudden cardiac death compared to troponin complex mutation carriers (p=0.01). Limitations of this study included heterogeneity in usage of baseline versus extended gene panels administered to patients.

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. 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.

A study conducted by Restrepo-Cardoba et al (2017) assessed the utility of genetic testing in patients with diagnosed HCM classified with poor (Group A) or favorable (Group B) clinical course.[40] Poor clinical course was defined as occurrence of a sudden cardiac death event, an appropriate implantable cardioverter-defibrillator discharge, and/or a required heart transplant for end-stage heart failure. Forty-five pathogenic mutations were identified in 28 (56%) patients in Group A and in 23 (46%) from Group B (p=0.317). Only 40 patients (40%) demonstrated pathogenic mutations that were previously reported in the literature and only 15 (15%) had pathogenic mutations that were reported in ≥10 individuals. Four out of the 46 pathogenic mutations identified (8%) could have been considered as associated with poor prognosis based on published information. Pathogenic mutations associated with poor prognosis were detected in only 5 patients in Group A (10%). Additionally, mutations considered to confer a benign prognosis were detected in 3 patients (6%). By contrast, pathogenic mutations were identified in 3 patients (6%) and mutations considered to confer a benign prognosis were detected in 4 patients (8%) with a favorable clinical course in Group B. Therefore, study authors concluded that genetic findings were not useful to predict prognosis in most HCM patients.

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 an 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 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 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.

SUPPLEMENTAL INFORMATION

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

Clinical input was solicited by Blue Cross Blue Shield Association 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

Heart Failure Society of America

In 2018, the Heart Failure Society of America established practice guidelines on the genetic evaluation of cardiomyopathy via a joint writing group with the American College of Medical Genetics.[40] The expert panel issued the following recommendations related to genetic testing (see Table 3).

Table 3. Guidelines on Genetic Testing in Hypertrophic Cardiomyopathy

Recommendations	LOE
Genetic testing is recommended for the most clearly affected family member	A[1]
Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants	A[1]
In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered	A[1]

LOE: level of evidence.
1 Level A evidence indicates genetic evaluation or testing has a high correlation with the cardiomyopathic disease of interest in studies with a moderate or large sample size. Levels of evidence were assigned based on literature review and full consensus of the writing group's expert opinion.

The practice guidelines recommend medical and device therapies based on cardiac clinical phenotypes.

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 4):[42]

Table 4. Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy

Recommendations	COR	LOE
Genetic counseling is recommended for all patients with hypertrophic cardiomyopathy 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	I	B
Genetic testing is recommended in patients fulfilling diagnostic criteria for hypertrophic cardiomyopathy when it enables cascade genetic screening of their relatives	I	B
It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations	I	C
In the presence of symptoms and signs of disease suggestive of specific causes of hypertrophic cardiomyopathy, genetic testing is recommended to confirm the diagnosis	I	B
Cascade genetic screening, after pre-test counseling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation	I	B
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	I	C
Genetic counseling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team	IIa	C
Genetic testing in patients with a borderline diagnosis of hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy, 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
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.

In 2019,O'Mahony et al published a meta-analysis assessing the effectiveness of the 2014 European Society of Cardiology guideline on sudden cardiac death in HCM relating to the use of the novel HCM Risk-SCD risk prediction model to guide use of implantable cardioverter-defibrillators.[43] This tool, which utilizes clinical parameters and family history of sudden cardiac death, was found to provide accurate risk estimations. From a study cohort of 7291 individuals (70% low-risk, 15% intermediate-risk, 15% high-risk), the pooled prevalence of sudden cardiac death endpoints was 1.01% (95% confidence interval [CI], 0.52 to 1.61) in low-risk patients, 2.43% (95% CI, 1.23 to 3.92) in intermediate-risk patients, and 8.4% (95% CI, 6.68 to 10.25) in high-risk patients.

American College of Cardiology and American Heart Association

The American College of Cardiology and the American Heart Association issued updated joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy in 2020.[44] Table 5 lists the recommendations on genetic testing.

Table 5. 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. In patients with HCM, evaluation of familial inheritance, including a 3-generation family history, is recommended as part of the initial assessment.	I1	BB-NR
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. In patients with HCM, genetic testing is beneficial to elucidate the genetic basis to facilitate the identification of family members at risk for developing HCM (cascade testing).	I1	BB-NR
In patients with an atypical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended 1	1	B-NR

In patients with HCM who choose to undergo genetic testing, pre- and posttest genetic counseling by an expert in the genetics of cardiovascular disease is recommended so that risks, benefits, results, and their clinical significance can be reviewed and discussed with the patient in a shared decision-making process	1	B-NR
When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM.	1	B-NR
In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered.	1	B-NR
In families where a sudden unexplained death has occurred with a postmortem diagnosis of HCM, postmortem genetic testing is beneficial to facilitate cascade genetic testing and clinical screening in first-degree relatives.	1	B-NR
In patients with HCM who have undergone genetic testing, serial reevaluation of the clinical significance of the variant(s) identified is recommended to assess for variant reclassification, which may impact diagnosis and cascade genetic testing in family members	1	B-NR
In affected families with HCM, preconception and prenatal reproductive and genetic counseling should be offered.	1	B-NR
In individuals who are genotype-positive, phenotype-negative for HCM, serial clinical assessment, ECG, and cardiac imaging are recommended at periodic intervals depending on age (every 1 to 2 years in children and adolescents, and every 3 to 5 years in adults) an change in clinical status	1	B-NR
In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable.	2a	C-LD
In patients with HCM, the usefulness of genetic testing in the assessment of risk of sudden cardiac death is uncertain.	2b	B-NR
In patients with HCM who harbor a variant of uncertain significance, the usefulness of clinical genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain.	2b	B-NR
For patients with HCM who have undergone genetic testing and were found to have no pathogenic variants (i.e., harbor only benign/likely benign variants), cascade genetic testing of the family is not useful.	3	B-NR
Ongoing clinical screening is not indicated in genotype-negative relatives in families with genotype-positive HCM, unless the disease-causing variant is downgraded to variant of uncertain significance, likely benign, or benign variant during follow-up.	3	B-NR
In individuals who are genotype-positive, phenotype-negative for HCM, ICD is not recommended for primary prevention.	3	B-NR

COR: class of recommendation; HCM: hypertrophic cardiomyopathy; LOE: level of evidence; SCD: sudden cardiac death.

In 2015, the American College of Cardiology and American Heart Association issued a joint scientific statement on the eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities.[45] Fifteen Task Forces were assigned to review the scientific evidence for various cardiovascular diseases and with expert consensus, develop recommendations for athletic participation. Table 6 outlines the recommendations related to HCM.[46]

Table 6. ACC/AHA Recommendations for Participation in Sports

Recommendations	COR	LOE
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.	IIa	C
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).	III	C

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 published recommendations for genetic testing for cardiac channelopathies and cardiomyopathies in 2011.[47] These recommendations were reaffirmed in 2018 and will be formally reassessed by 2023. 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 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00156429	Genetic Predictors of Outcome in hypertrophic cardiomyopathy Patients	540	May 2020
NCT04036799	PRecIsion Medicine in CardiomyopathY (PRIMaCY)	3000	Dec 2020
NCT02432092	Pediatric Cardiomyopathy Mutation Analysis	300	Apr 2021
NCT01915615	hypertrophic cardiomyopathy R - Novel Markers of Prognosis in Hypertrophic Cardiomyopathy	2750	Apr 2022
NCT01736566	The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine	213	Aug 2022
NCT03846297	Optimisation of Decision Making for Defibrillator Implantation in Hypertrophic Cardiomyopathy	2000	Mar 2026
Unpublished			
NCT03726424	The Clinical Outcome and Prognosis of Patients With Different Pathogenic Mutations of Hypertrophic Cardiomyopathy	1000	Dec 2019 (unknown)

NCT: national clinical trial

Government Regulations
National/Local:

There is no national or local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing – Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/09	1/29/08	12/9/08	Joint policy established
3/1/12	12/13/11	12/21/11	Routine maintenance, changed policy title; additional references added, reformatted to match BCBSA.
11/1/13	8/22/13	8/27/13	Routine maintenance, no change in policy status, Added CPT codes 81405-81407 and 81479
5/1/15	2/17/15	2/27/15	Routine maintenance Updated rationale and references
5/1/16	2/16/16	2/16/16	Policy updated with literature review; references added. No change in policy status.
5/1/17	2/21/17	2/21/17	Added code 81439 as established. Routine policy maintenance.
5/1/18	2/20/18	2/20/18	Rationale restructured, reference # 9 added. No change in policy status.
5/1/19	2/19/19		Rationale reformatted, references 1, 3, and 21-28 added. No change in policy status.
5/1/20	2/18/20		Updated rationale, added references # 29-32 and 37. No change in policy status.
5/1/21	2/16/21		Rationale update, added references 30, 36-39, 42-44. No change in policy status.
5/1/22	2/15/22		Added reference # 27, no change in policy status.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR INHERITED HYPERTROPHIC CARDIOMYOPATHY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.