

Medical Policy



Title: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

<i>Related Policies:</i>	<ul style="list-style-type: none"> ▪ <i>Genetic Testing For Cardiac Ion Channelopathies</i> ▪ <i>General Approach To Evaluating The Utility Of Genetic Panels</i>
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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • Who are asymptomatic with risk for hypertrophic cardiomyopathy because of a positive family history 	Interventions of interest are: <ul style="list-style-type: none"> • Testing for specific hypertrophic cardiomyopathy-related variant identified in affected family member(s) 	Comparators of interest are: <ul style="list-style-type: none"> • Clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Test accuracy • Test validity • Changes in reproductive decision making • Symptoms • Morbid events

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are asymptomatic with risk for hypertrophic cardiomyopathy because of a positive family history 	Interventions of interest are: <ul style="list-style-type: none"> Nonspecific testing for hypertrophic cardiomyopathy–related variant 	Comparators of interest are: <ul style="list-style-type: none"> Clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Test accuracy Test validity Changes in reproductive decision making Symptoms Morbid events

DESCRIPTION

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition that is caused by a 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.

OBJECTIVE

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

BACKGROUND

Familial Hypertrophic Cardiomyopathy

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

The genetic basis for hypertrophic cardiomyopathy 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.^{5,6,7,8} 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 hypertrophic cardiomyopathy. 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 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. These 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 hypertrophic cardiomyopathy is made.

Hypertrophic cardiomyopathy is a very heterogeneous disorder. Manifestations range from subclinical, asymptomatic disease to severe, life-threatening disease. Wide phenotypic variability exists among individuals, even when an identical variant is present, including among affected family members.² This variability in clinical expression may be related to environmental factors and modifier genes.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 heart failure 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 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 variant in the family, analyzes the genes most commonly associated with genetic variants for hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy and those associated with other cardiac disorders. For example, the Pan Cardiomyopathy panel (Laboratory for Molecular Medicine) is a next-generation sequencing panel of 62 genes associated with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, left ventricular noncompaction syndrome, Danon syndrome, Fabry disease, Brugada 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 determine the pathogenicity of genetic variants associated with hypertrophic cardiomyopathy. 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 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 1 variant that is thought to be pathogenic is increasing. A 2013 study reported that 9.5% (19/200) of patients from China with hypertrophic cardiomyopathy had multiple pathogenic variants and that the number of variants correlated with severity of disease.¹⁶

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 (CLIA). Sequencing tests for hypertrophic cardiomyopathy are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

No assay kits have been approved by the FDA for genetic testing for hypertrophic cardiomyopathy.

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.

POLICY

- A. Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered **medically necessary** for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene variant present in that affected relative (see Policy Guidelines).
- B. Genetic testing for predisposition to HCM is considered **not medically necessary** for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathogenic variants.
- C. Genetic testing for predisposition to HCM is considered **experimental / investigational** for all other patient populations, including, but not limited to, individuals who have a first-degree relative with clinical HCM, but in whom genetic testing is unavailable.

Policy Guidelines

1. Due to the complexity of genetic testing for HCM and the potential for misinterpretation of results, the decision to test and the interpretation of test results should be performed by, or in consultation with, an expert in the area of medical genetics and/or hypertrophic cardiomyopathy.
2. To inform and direct genetic testing for at-risk individuals, genetic testing should initially be performed in at least 1 close relative with definite HCM (index case), if possible.
3. Because there are varying degrees of penetrance for different HCM variants, consideration for testing of second- or third-degree relatives may be appropriate in certain circumstances. Some judgment should be allowed for these decisions, for example, in the case of a small family pedigree. Consultation with an expert in medical genetics and/or the genetics of HCM, in conjunction with a detailed pedigree analysis, is appropriate when testing of second- or third- degree relatives is considered.
4. Genetic Counseling: Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
5. Genetics Nomenclature Update: The Human Genome Variation Society 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). HGVS nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 29, 2021.

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 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 HYPERTROPHIC CARDIOMYOPATHY RELATED VARIANT

Clinical Context and Test Purpose

The purpose of targeted genetic testing of patients who are asymptomatic but at-risk of hypertrophic cardiomyopathy is to inform management decisions. Genetic testing for hypertrophic cardiomyopathy 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: Does testing an asymptomatic individual for a variant known to be associated with hypertrophic cardiomyopathy identified in a family member improve 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 hypertrophic cardiomyopathy and a known pathogenic variant.

Interventions

The test being considered is targeted genetic testing for the variant(s) identified in the relative with hypertrophic cardiomyopathy.

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 hypertrophic cardiomyopathy.

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 hypertrophic cardiomyopathy.

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.

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.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for inherited hypertrophic cardiomyopathy, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy or will develop hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy in the future.

Multiple studies have been published on the phenotypic penetrance of hypertrophic cardiomyopathy, 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 hypertrophic cardiomyopathy. 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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy in such patients. Survival in those with hypertrophic cardiomyopathy due to variants in the *MYH7* gene varies considerably despite nearly complete disease penetrance and significant hypertrophy.^{19,20,21}
- Variants in the *TNNI3* gene are found in 2% to 7% of patients with hypertrophic cardiomyopathy 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 $\leq 4\%$ of patients with hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy 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, hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy at initial assessment. After 3.5 years of follow-up, 2 of the phenotype negative genotype positive children developed hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy.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, hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy at baseline, all-cause mortality was 0.1% and hypertrophic cardiomyopathy 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 Hypertrophic Cardiomyopathy Variants

Study	Design	Population	Number with HCM Diagnosis after Variant Detection and Cardiac Evaluation (%)	Follow-up, years	Number with HCM Diagnosis after Follow-up (%)
Michels et al (2009) ²⁴	Case series	Asymptomatic relatives who tested	31 (41)	0	NA

Study	Design	Population	Number with HCM Diagnosis after Variant Detection and Cardiac Evaluation (%)	Follow-up, years	Number with HCM Diagnosis after Follow-up (%)
		positive for a hypertrophic cardiomyopathy variant (n=76)			
Cardoso et al (2017) ²⁵ ,	Case series	Asymptomatic child relatives who tested positive for a hypertrophic cardiomyopathy variant (n=14)	7 (50)	3.5	2 (28)
van Velzen et al (2018) ²⁶ ,	Retrospective cohort	Asymptomatic relatives who tested positive for a hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy and known variants.

Ko et al (2018) conducted a survey of patients with hypertrophic cardiomyopathy with and without variants and assessed first-degree family members for development of hypertrophic cardiomyopathy related adverse events.²⁸ Patients were recruited from a registry of patients with hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy diagnosis. Among patients without genetic variants and no prior family history, 2 of 64 first degree relatives who were screened reported a hypertrophic cardiomyopathy diagnosis.

Lopes et al (2018) conducted genotype-phenotype analyses of probands and relatives (N=424) in the Portuguese registry of hypertrophic cardiomyopathy.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 hypertrophic cardiomyopathy, 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 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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy. 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 hypertrophic cardiomyopathy 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 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 a Meta-Analysis of Studies Assessing Genetic Variants in Patients with Hypertrophic Cardiomyopathy

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

CI: confidence interval

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 hypertrophic cardiomyopathy, although it makes hypertrophic cardiomyopathy more likely. Several studies that followed relatives who tested positive for a hypertrophic cardiomyopathy variant, reported that hypertrophic cardiomyopathy 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, more effective therapy, or avoid unnecessary therapy or 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 hypertrophic cardiomyopathy 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 1 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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy can be discontinued. Additionally, 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 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 Hypertrophic Cardiomyopathy Related Variant

Use of genetic testing for hypertrophic cardiomyopathy has the greatest utility in asymptomatic family members of patients with hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy and allow a reduction in surveillance for complications. Detection of variants in asymptomatic carriers may lead to the adoption of hypertrophic cardiomyopathy 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 HYPERTROPHIC CARDIOMYOPATHY RELATED VARIANT

Clinical Context and Test Purpose

The purpose of nonspecific genetic testing of patients who are asymptomatic but at-risk of hypertrophic cardiomyopathy is to inform management decisions. Genetic testing for hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy?

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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy.

Outcomes

The potential beneficial outcome of primary interest would be a reduction in surveillance for the development of hypertrophic cardiomyopathy. 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.

The appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of hypertrophic cardiomyopathy 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.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for inherited hypertrophic cardiomyopathy, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)

- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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

Case Series

Evidence of clinical sensitivity (i.e., the probability that a person with clinical hypertrophic cardiomyopathy, or who will get hypertrophic cardiomyopathy, will have a positive genetic test result) consists of several case series of patients with established hypertrophic cardiomyopathy. To date, the published variant detection rates range from 33% to 67%,^{19,22,32,33,34,35} 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 hypertrophic cardiomyopathy, 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, unidentified, genes may be responsible for hypertrophic cardiomyopathy. Finally, there may be unknown, nongenetic factors that mimic hypertrophic cardiomyopathy. Variant detection rates will likely improve over time with recognition of new variants.

Ingles et al (2018) identified 24 gene panels for hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy 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 with limited or no evidence causes potential harm to patients who may experience anxiety over results and undergo unnecessary surveillance or treatment.

Observational Studies

Data from patients diagnosed with hypertrophic cardiomyopathy in the Sarcomeric Human Cardiomyopathy Registry (SHaRe) (N=4591; 12% with affected relatives; 35% with a family history of hypertrophic cardiomyopathy) 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 hypertrophic cardiomyopathy family history (58% vs. 25%; $p<0.001$).

Maurizi et al (2018) assessed long-term outcomes of pediatric-onset hypertrophic cardiomyopathy and age-specific risk factors for lethal arrhythmic events.³⁸ Of 1644 patients with hypertrophic cardiomyopathy 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 event 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 hypertrophic cardiomyopathy patients to construct a score to predict the genetic yield and improve counseling.³⁹ Unrelated patients with hypertrophic cardiomyopathy (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 of <45 years, familial hypertrophic cardiomyopathy, 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 hypertrophic cardiomyopathy 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, more effective therapy, or avoid unnecessary therapy or 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 hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy 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 a hypertrophic cardiomyopathy related variant.

Section Summary: Nonspecific Testing for a Hypertrophic Cardiomyopathy 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 hypertrophic cardiomyopathy. 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 because of a positive family history who receive testing for a specific hypertrophic cardiomyopathy related variant identified in affected family member(s), 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. For individuals at-risk for hypertrophic cardiomyopathy (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 a hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy and thus has a similar risk of developing hypertrophic cardiomyopathy as the general population. Such patients will no longer need ongoing surveillance

for the presence of clinical signs of hypertrophic cardiomyopathy. 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 an improvement in the net health outcome.

For individuals who are asymptomatic with risk for hypertrophic cardiomyopathy because of a positive family history who receive nonspecific testing for a hypertrophic cardiomyopathy 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 hypertrophic cardiomyopathy 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

2011 Input

Clinical input was sought to help determine whether the use of genetic testing for predisposition to inherited hypertrophic cardiomyopathy would provide an improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, input was received while this policy was under review in 2011. Input was solicited in January 2011 and provided general agreement with the policy. Additional clinical input in October 2011 was sought to address specific questions. The initial vetting indicated uniform agreement with the medically necessary indication for individuals with a first-degree relative who has a known pathogenic variant. The restriction to first-degree relatives was questioned with mixed responses; 2 reviewers indicated that they agreed with testing only first-degree relatives, 2 reviewers indicated that testing should be offered to non-first-degree relatives, and 1 reviewer was undecided.

The second round of clinical input 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 1 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).

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.⁴¹ The expert panel issued the following recommendations related to genetic testing (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.

European Society of Cardiology

In 2014, the European Society of Cardiology issued guidelines on the diagnosis and management of hypertrophic cardiomyopathy, which included the following recommendations related to genetic testing (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

Recommendations	COR	LOE
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 ^{3/4} following pre-test family counseling ^{3/4} 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; 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 hypertrophic cardiomyopathy relating to the use of the novel hypertrophic cardiomyopathy risk sudden cardiac death risk prediction model to guide use of implantable cardioverter-defibrillators⁴³. 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

In 2020, the American College of Cardiology Foundation and the American Heart Association issued updated joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy.⁴⁴ Table 5 lists the recommendations on genetic testing.

Table 5. Joint Guidelines on Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Recommendations	COR	LOE
In patients with HCM, evaluation of familial inheritance, including a 3-generation family history, is recommended as part of the initial assessment.	1	B-NR
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).	1	B-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	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) and 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; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LOE: level of evidence.

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 hypertrophic cardiomyopathy.⁴⁶

Table 6. American College of Cardiology/American Heart Association 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

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

Heart Rhythm Society and the European Heart Rhythm Association

In 2011, the Heart Rhythm Society and the European Heart Rhythm Association published joint recommendations on genetic testing for cardiac channelopathies and cardiomyopathies.⁴⁷ These recommendations were reaffirmed in 2018 and will be formally reassessed by 2023. For hypertrophic cardiomyopathy (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

Ongoing and Unpublished Clinical Trials

Some currently ongoing and 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
<i>Ongoing</i>			
NCT04036799	Development of a Risk Calculator to Predict Sudden Cardiac Death With Hypertrophic Cardiomyopathy	3000	Dec 2020
NCT02432092	Pediatric Cardiomyopathy Mutation Analysis	300	Apr 20 28
NCT01915615	HCMR - 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 202 7
<i>Unpublished</i>			
NCT03726424	The Clinical Outcome and Prognosis of Patients With Different Pathogenic Mutations of Hypertrophic Cardiomyopathy	1000	Dec 2019 (unknown)

NCT: national clinical trial.

CODING

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

CPT/HCPCS

- 81403 Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
- 81405 Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
- 81406 Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
- 81407 Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)

- 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, and TTN)
- 81479 Unlisted molecular pathology procedure
- 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

ICD-10 Diagnoses

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

REVISIONS

03-26-2012	Policy added to the bcbsks.com web site.
04-08-2013	Posted to the web site on 03-08-2013 to give 30 days notice to professional and institutional providers.
	Description section updated
	Rationale section updated
	<ul style="list-style-type: none"> ▪ In Coding section: Added CPT codes: 81405, 81406, 81407, 81479 (effective 01-01-2013) Updated coding notations. Added Diagnosis codes 425.11, 425.4, V17.41, V17.49, V82.719, V82.79 which had been erroneously left off the policy. Removed the phrase "Experimental / Investigational on all diagnoses related to this medical policy." which had been incorrectly placed on the policy.
	References updated
12-31-2013	<ul style="list-style-type: none"> ▪ In Coding section: Nomenclature updated on CPT codes: 81405, 81406 ICD-10 Diagnoses added.
03-31-2015	Description section updated
	Rational section updated
	In Coding section: <ul style="list-style-type: none"> ▪ Updated bulleted coding directions
	References updated
01-01-2016	In Coding section: <ul style="list-style-type: none"> ▪ Updated CPT code 81405 nomenclature
	Updated References section.
02-17-2016	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item B, added "with established HCM" to read "Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathologic mutations. ▪ In Policy Guidelines, added Item 4 on genetic counseling.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT code 81403.
	Updated References section.
	Added Appendix section.

01-01-2017	In Coding section: <ul style="list-style-type: none"> Added CPT code 81439 (<i>New code, effective January 1, 2017</i>).
04-12-2017	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> In Item A, added "variant" and removed "mutation" and "section" to read, "Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) may be considered medically necessary for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene variant present in that affected relative (see Policy Guidelines)." In Item B, added "variants" and removed "mutation" to read, "Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathologic variants." In Policy Guidelines, added Item 5.
	Updated Rationale section.
	Updated References section.
	Updated Appendix section.
01-01-2018	In Coding section: <ul style="list-style-type: none"> Revised nomenclature to CPT code: 81439. Removed ICD-9 codes.
05-11-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> In Item B, removed "pathologic" and added "pathogenic" to read, "Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathogenic variants." Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> Updated coding bullets.
	Updated References section.
	Removed Appendix section.
04-24-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
05-05-2021	Updated Description section.
	Updated Rationale section.
	Updated References section.

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