

Medical Policy



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Title: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Professional

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

DESCRIPTION

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

OBJECTIVE

The objective of this policy 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 (HCM) 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 (SCD) 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 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 (ie, 1 amino acid is replaced for another), and the strongest evidence for pathogenicity is available for 11 genes coding for thick filament proteins (*MYH7*, *MYL2*, *MYL3*), thin filament proteins (*TNNT2*, *TNNI3*, *TNNC1*, *TPM1*, *ACTC*), intermediate filament proteins (*MYBPC3*), and the Z-disc adjoining the sarcomere (*ACTN2*, *MYOZ2*). Variants in myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) are the most common and account for roughly 80% of sarcomeric HCM. These genetic defects are inherited in an autosomal dominant pattern with rare exceptions.⁴ In patients with clinically documented HCM, 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 HCM depends on the presence of left ventricular hypertrophy, measured by echocardiography or magnetic resonance imaging, in the absence of other known causative factors such as valvular disease, long-standing hypertension, or another myocardial disease.⁶ In addition to primary cardiac disorders, there are systemic diseases that can lead to left ventricular hypertrophy and thus mimic HCM. They include infiltrative diseases such as amyloidosis, glycogen storage diseases (eg, Fabry disease, Pompe disease), and neuromuscular disorders (eg, Noonan syndrome, Friedreich ataxia).⁹ These disorders need to be excluded before a diagnosis of familial HCM is made.

HCM is a very heterogeneous disorder. Manifestations range from subclinical, asymptomatic disease to severe, life-threatening disease. Wide phenotypic variability exists among individuals, even when an identical variant is present, including among affected family members.² This variability in clinical expression may be related to environmental factors and modifier genes.¹⁰ A large percentage of patients with HCM, 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 SCD. A subset of patients has severe disease that causes a major impact on quality of life and life expectancy. Severe disease can lead to disabling symptoms, as well as complications of HCM, including heart failure and malignant ventricular arrhythmias. Symptoms and presentation may include SCD due to unpredictable ventricular tachyarrhythmias, heart failure, or atrial fibrillation, or some combination.¹¹

Management of patients with HCM involves treating cardiac comorbidities, avoiding therapies that may worsen obstructive symptoms, treating obstructive symptoms with β -blockers, calcium channel blockers, and (if symptoms persist) invasive therapy with surgical myectomy or alcohol ablation, optimizing treatment for heart failure, if present, and SCD risk stratification. Implantable cardioverter defibrillator implantation may be indicated if there is a family history of SCD.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for screening clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals ages 12 to 18 years and every 3 to 5 years for adults.¹⁰ Additional screening is recommended for any change in symptoms that might indicate the development of HCM.¹⁰

Genetic Testing

Genetic testing has been proposed as a component of screening at-risk individuals to determine predisposition to HCM among those patients at risk. Patients at risk for HCM are defined as individuals who have a close relative with established HCM. Results of genetic testing may influence the management of at-risk individuals, which may, in turn, lead to improved outcomes. Furthermore, results of genetic testing may have implications for decision making in the areas of reproduction, employment, and leisure activities. However, the likelihood of obtaining a positive genetic test in the proband is only about 50% because all genes causing HCM have not yet been identified or are absent from testing panels. Failure to identify the causative variant in the proband is an indeterminate result that provides no useful information and precludes predictive testing in 33% to 67% of cases.

Commercial testing has been available since 2003, and numerous companies offer genetic testing for HCM.^{5,12-15} Testing is performed either as a comprehensive or targeted gene test. Comprehensive testing, which is done for an individual without a known

genetic variant in the family, analyzes the genes most commonly associated with genetic variants for HCM and evaluates whether any potentially pathogenic variants are present. Some available panels include testing for multisystem storage diseases that may include cardiac hypertrophy, such as Fabry disease (*GLA*), familial transthyretin amyloidosis (*TTR*), and X-linked Danon disease (*LAMP2*).

Other panels include testing for genes related to HCM and those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen) is a next-generation sequencing panel of 44 genes associated with HCM, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, left ventricular noncompaction syndrome, Danon syndrome, Fabry disease, Barth syndrome, and transthyretin amyloidosis.¹⁶

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

It can be difficult to determine the pathogenicity of genetic variants associated with HCM. Some studies have reported that assignment of pathogenicity has a relatively high error rate and that classification changes over time.^{17,18} With next-generation sequencing and whole-exome sequencing techniques, the sensitivity of identifying variants on the specified genes has increased substantially. At the same time, the number of variants of uncertain significance is also increased with next-generation sequencing. Also, the percentage of individuals who have more than 1 variant that is thought to be pathogenic is increasing. A 2013 study reported that 9.5% (19/200) patients from China with HCM had multiple pathogenic variants and that the number of variants correlated with severity of disease.¹⁹

REGULATORY STATUS

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

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

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 was created in December 2011 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through January 8, 2018.

This review was informed by a TEC Assessment (2009).²⁰ That TEC Assessment reviewed the evidence on the accuracy of genetic testing in identifying patients who would subsequently develop hypertrophic cardiomyopathy (HCM) and identified 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 of patients who are asymptomatic but at risk of HCM is to inform management decisions. Genetic testing for HCM would play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

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

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

Patients

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

Interventions

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

Comparators

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

Outcomes

If the test has a high negative predictive value, the main beneficial outcome would be to safely reduce or eliminate the need for routine clinical surveillance for signs and symptoms of HCM.

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

Timing

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

Setting

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

Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable

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

Clinically Valid

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

When a patient tests positive for a specific HCM-related variant, the clinical validity of a test to detect that specific variant in an asymptomatic first-degree relative relies on 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 60.²¹
- Variants in the *MYH7* gene are found in 13% to 25% of patients with HCM and are associated with a high penetrance of disease, younger age at diagnosis, and more severe hypertrophy. However, there is substantial clinical heterogeneity in the phenotypic expression of HCM in such patients. Survival in those with HCM due to variants in *MYH7* gene varies considerably despite nearly complete disease penetrance and significant hypertrophy.²²⁻²⁴
- Variants in the *cTnI* gene are found in 2% to 7% of patients of HCM with a disease penetrance of approximately 50%.^{22,25,26}

Studies relating to clinical validity are summarized below.

- Michels et al (2009) analyzed 76 asymptomatic family members who underwent predictive genetic testing based on 32 probands with a known variant.²⁷ Of the 76 asymptomatic family members, HCM was diagnosed in 31 (41%) cases based on published diagnostic criteria for HCM in adult members.
- 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).²⁸

Section Summary: Clinically Valid

The available evidence suggests that, in cases where there is interest in identifying a specific variant (ie, when there is a known variant in an affected family member, testing can rule in or rule out the presence of 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.

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.^{6,19} 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.

Section Summary: Testing for a Specific HCM-Related Variant

Use of genetic testing for HCM has the greatest utility in asymptomatic family members of patients with HCM who have a known genetic variant. Given the high sensitivity for *known* variants, the absence of a variant in the asymptomatic relatives should rule out the presence of familial HCM and allow a reduction in surveillance for complications. Detection of variants in asymptomatic carriers may lead to the adoption of HCM surveillance with cardiac imaging to detect the development of the phenotype and possible institution of therapy and lifestyle adaptations. Further, they may help in reproductive decision making, although direct evidence is limited on the impact of genetic information in this setting.

Nonspecific Testing for a HCM-Related Variant

Clinical Context and Test Purpose

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

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

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

Patients

The relevant population of interest 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.

Comparators

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

Outcomes

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

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

Timing

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

Setting

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

Technically Reliable

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

Clinically Valid

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

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

Evidence of clinical sensitivity (the probability that a person with clinical HCM, or who will get HCM, will have a positive genetic test result), consists of several case series of patients with established HCM. To date, the published variant detection rates range from 33% to 67%,^{22,25,29-32} 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.

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.

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

Chain of Evidence

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

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

Section Summary: Nonspecific Testing for a HCM-Related Variant

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

SUMMARY OF EVIDENCE

For individuals who are asymptomatic with risk for HCM because of a positive family history who receive testing for a specific HCM-related variant identified in affected family member(s), the evidence includes studies reporting on the clinical validity of testing. 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 an 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.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

In response to requests, input was received while this policy was under review in 2011. Input was solicited in January 2011 on general agreement with the policy and again in October 2011 to address specific questions raised after the first round of vetting. The initial vetting indicated uniform agreement with the medically necessary indication for individuals with a first-degree relative who has a known pathogenic variant. This vetting also asked whether testing should be restricted to first-degree relatives. To this question, there was a mixed response, with 2 reviewers indicating that they agreed with testing only first-degree relatives, 2 reviewers indicating that testing should be offered to non-first-degree relatives, and 1 reviewer who was unsure.

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

European Society of Cardiology

In 2014, the European Society of Cardiology issued guidelines on the diagnosis and management of HCM, which included the following recommendations related to genetic testing (see Table 1).³³

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

Recommendations	COR	LOE
Genetic counselling is recommended for all patients with HCM when their disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members	I	B

Recommendations	COR	LOE
Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM 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 HCM, genetic testing is recommended to confirm the diagnosis	I	B
Cascade genetic screening, after pre-test counselling, 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 counselling 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 HCM should be performed only after detailed assessment by specialist teams	IIa	C
Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives	IIa	C
First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family	IIa	B
When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2-5 years (or 6-12 monthly if non-diagnostic abnormalities are present)	IIa	C
The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing—following pre-test family counselling—when they are aged 10 or more years, and this should be carried out in accordance with international guidelines for genetic testing in children	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 counselling by experienced physicians and when it is agreed to be in the best interests of the child	IIb	C
When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical or genetic testing of first-degree child relatives before the age of 10 years may be considered	IIb	C
In definite mutation carriers who have no evidence of disease expression, sports activity may be allowed after taking into account the underlying mutation and the type of sports activity, and the results of regular and repeated cardiac examinations	IIb	C

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

American College of Cardiology Foundation and the American Heart Association

The American College of Cardiology Foundation and the American Heart Association issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy in 2011.¹¹ Table 2 lists the recommendations on genetic testing.

Table 2. Joint Guidelines on Diagnosis and Treatment of HCM

Recommendations	COR	LOE
Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM	I	B
Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient	I	B
Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM	I	B
Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause	I	B

Recommendations	COR	LOE
Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM	IIa	B
The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain	IIb	B
Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation	III	B
Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM	III	B

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

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 2011.³⁴ For hypertrophic cardiomyopathy, the following recommendations (both class I) were made:

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01915615	HCMR - Novel Markers of Prognosis in Hypertrophic Cardiomyopathy	2750	Nov 2018
NCT00156429	Genetic Predictors of Outcome in HCM Patients	540	May 2020

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 (eg, 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 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

- 81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
- 81407 Molecular pathology procedure, Level 8 (eg, 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 (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, 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

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

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.
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.

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