Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Effective: April 1, 2019

Next Review: February 2020
Last Review: February 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition that is caused by a mutation 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 mutations is currently available through a number of commercial laboratories.

MEDICAL POLICY CRITERIA

I.   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 and a known pathogenic HCM gene mutation.

II. 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* has tested negative for pathologic mutations.

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

*Note: First-degree relatives: parents, siblings, and children of an individual

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   o History and physical exam including any relevant diagnoses related to the genetic testing
   o Conventional testing and outcomes
   o Conservative treatments, if any

CROSS REFERENCES

1. [Genetic Testing for Cardiac Ion Channelopathies](#), Genetic Testing, Policy No. 07
2. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
3. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
4. [Implantable Cardioverter Defibrillator](#), Surgery, Policy No. 17

BACKGROUND

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

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 a number of different protein structures.[5] Nearly 1400 individual mutations in at least 18 different genes have been identified to date.[6-8] Approximately 90% of pathogenic mutations are missense (i.e., one 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*). Mutations in myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) are the most common and account for roughly 80% of sarcomeric HCM. These genetic defects are inherited in an autosomal dominant pattern with rare exceptions.[5] Genetic abnormalities can be identified in approximately 60% of patients with clinically

documented HCM.[7,9] Most patients demonstrate a familial pattern of disease, although some exceptions are found, presumably due to *de novo* mutations.[9]

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

HCM is a very heterogenous disorder. Manifestations range from subclinical, asymptomatic disease to severe life-threatening disease. Wide phenotypic variability exists among individuals, even when an identical mutation 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 of all HCM patients, 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 beta 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.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals between the ages of 12 to 18 years and every three to five years for adults.[10] Additional screening is recommended for any change in symptoms that might indicate the development of HCM.[10] Results of genetic testing may influence management of these at-risk individuals, which may in turn lead to improved outcomes. Furthermore, results of genetic testing may have implications for decision making in the areas of reproduction, employment, and leisure activities.

Commercial testing has been available since May 2003, and there are numerous commercial companies that currently offer genetic testing for HCM.[6,12-15] Testing is performed either as comprehensive testing or targeted gene testing. Comprehensive testing, which is done for an individual without a known genetic mutation in the family, analyzes the genes that are most commonly associated with genetic mutations for HCM and evaluates whether any potentially pathogenic mutations are present. The number of HCM genes in the testing panel ranges between 12 and 18.[6] For a patient with a known mutation in the family, targeted testing is performed. Targeted mutation testing evaluates the presence or absence of a single mutation known to exist in a close relative.

There can be difficulties in determining the pathogenicity of genetic variants associated with HCM. Some studies have reported that assignment of pathogenicity has a relatively high error rate and that classification changes over time.[16,17] With next-generation and whole-exome sequencing techniques, the sensitivity of identifying variants in the specified genes has increased substantially. At the same time, the number of variants of unknown significance has also increased with next-generation sequencing. Also, the percent of individuals who have more than one mutation that is thought to be pathogenic is increasing. A study in 2013 reported that 9.5% (19/200) patients with HCM had multiple pathogenic mutations and that the number of mutations correlated with severity of disease.[18]

REGULATORY STATUS

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for genetic testing for HCM, nor are any kits being actively manufactured and marketed for distribution. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. While FDA has technical authority to regulate home-brew tests, there is currently no active oversight or any known plans to begin oversight. Home-brew tests may be developed using reagents prepared in-house or, if available, commercially manufactured analyte-specific reagents (ASRs). ASRs are single reagents "intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens" and must meet certain FDA criteria but are not subject to premarket review.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[19] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

For predispositional genetic testing, the analytic validity (ability to detect or exclude a *specific* mutation identified in another family member) and clinical validity (ability to detect *any* pathologic mutation in a patient with HCM and exclude a mutation in a patient without HCM) were evaluated. The analytic validity is more relevant when there is a known mutation in the

family, whereas the clinical validity is more relevant for individuals without a known mutation in the family.

ANALYTIC VALIDITY

The analytic sensitivity (probability that a test will detect a specific mutation that is present) of sequence analysis for detecting mutations that cause HCM is likely to be very high based on what is known about the types of mutations that cause HCM and the limited empiric data provided by the manufacturer and detailed description of the testing methodology. There are fewer data available on the analytic specificity (probability that a test will be negative when a specific mutation is absent) of HCM testing. The available information on specificity, mainly from series of patients without a personal or family history of HCM, suggests that false-positive results for known pathologic mutations are uncommon.[20,21] However, the rate of false-positive results is likely to be higher for classification of previously unknown variants. There is some published evidence available on the analytic validity of next-generation sequencing (NGS) panels for genes associated with cardiomyopathies, including HCM. For example, one 17-gene panel was reported to have a maximum 96.7% sensitivity for single-nucleotide variants, with positive predictive values above 95%, compared with Sanger sequencing.[22]

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

CLINICAL VALIDITY

The clinical validity of genetic testing for HCM is considerably lower than the analytic validity, ranging from 33-67%. Evidence on clinical sensitivity, also called the mutation detection rate, consists of several case series of patients with established HCM.[23-26] This low detection rate may be due to testing methods, not-yet-identified HCM gene mutations, and nongenetic factors that mimic HCM.

Information about the pathogenicity of variants in HCM-associated genes is key to interpreting genetic test results. Manrai used publicly available data to identify and study variants that had previously been considered causal for HCM that were also overrepresented in the general population.[27] They discovered a number of patients, all of African or unspecified ethnicity, that had variants that were classified as pathogenic based on the understanding at the time the tests were done, but were now categorized as benign. These variants were more common among black Americans than white Americans. The results of this study highlight the importance of having sequence information from diverse populations to properly assess the potential pathogenicity of a variant.

Given the large size of many of the genes associated with HCM, particularly MYBPC3 and MYH7, the use of next generation sequencing (NGS) methods has been investigated as a more efficient way to evaluate for genetic mutations in HCM. NGS refers to one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. The use of next-generation sequencing and whole-exome sequencing has the potential to substantially increase the sensitivity. Small studies have demonstrated the potential role of these technologies in detecting recognized and novel mutations.[28-30]

Cardoso (2017) reported on the outcomes of 17 first-degree relatives of three probands. Of the 17 tested, 14 child relatives were variant carriers (70%; median age, 8 years) of whom seven (50%) were diagnosed with HCM at initial assessment. After 3.5 years of follow-up, two of the phenotype negative genotype positive children developed HCM at 10 and 15 years of age (28% penetrance rate).[31]

Gomez reported the yield of a two-step NGS process in a cohort of 136 patients with clinically diagnosed HCM.[32] In a validation cohort of 60 patients with both NGS results and prior identification of a mutation in MYH7, MYBPC3, TNNT2, TNNI3, ACTC1,TNNC1, MYL2, MYL3, or TPM1, sensitivity of NGS was 100% and specificity was 97% for single nucleotide variants and 80% for insertion or deletion variants. Among 76 clinically-diagnosed cases without previous genetic mutation testing, NGS identified 19 mutations.

Millat developed an NGS platform to evaluate the most common genetic mutations in a cohort of 75 patients with HCM and dilated cardiomyopathy.[33] The authors report very high analytic sensitivity (98.9%) for previously-detected mutations in the covered regions.

Rubattu used NGS to test for mutations in 17 HCM-related genes in a study of 70 HCM patients.[34] Of these, 35 had early-onset (≤25 years) and 35 had late-onset (≥65 years) disease. A total of 41 mutations were found, including seven novel mutations. The NGS mutation yield was significantly higher in individuals with early onset disease and in those with a family history of HCM.

Penetrance

The exact penetrance of HCM is unknown, with one review noting that not everyone with a deleterious mutation will develop manifestations of HCM.[35] However, a recent review indicated disease penetrance at approximately 100% with advanced age.[36] In addition, penetrance varies among different mutations and may even vary among different families with an identical pathologic mutation.[37,38] As a result, it is not possible to accurately estimate the penetrance for any given mutation in a specific family. Therefore, the identification of an HCM gene mutation does not always confer a diagnosis of HCM.

Clinical Predictors of a Mutation

A study by Ingles included 265 unrelated individuals with HCM, in which a total of 52% (138/265) had a mutation identified.[39] Mutations were more frequent in patients with an established family history of HCM than in those without a family history (72% vs 29%, p<0.001), and in those with a family history of sudden cardiac death (SCD) (89% vs 59%, p<0.001). Other predictors of finding a pathogenic mutation were female gender and increased left ventricular (LV) wall thickness.

Gruner derived a score for predicting the likelihood of finding a mutation, called the Toronto Hypertrophic Cardiomyopathy Genotype Score.[40] The score was developed using data from 471 consecutive patients referred for testing, of which 35% (163/471) were found to have a mutation. Independent predictors of a mutation that were incorporated into the model were age at diagnosis, female gender, arterial hypertension, positive family history, LV wall morphology, and LV posterior wall thickness.

An evaluation of a similar score, the Mayo Clinic Phenotype-Based Genotype Predictor Score, was published in 2016 by Murphy.[41] The score is calculated from six clinical and echocardiographic parameters and was developed to predict a positive genetic test for HCM.

This study tested the performance of the score in a validation cohort of 564 patients that received genetic counseling for a diagnosis of HCM at the Mayo Clinic between 2005 and 2014. Of these, 198 patients requested genetic testing, and 101 (51%) tested positive for an HCM-associated mutation. The genotype predictor score was significantly associated with a positive genetic test, according to Cochran-Armitage trend analysis (p < 0.0001).

Bos conducted a retrospective evaluation of 1053 patients with a clinical diagnosis of HCM and available HCM genetic testing for nine HCM-associated myofilament genes to develop a phenotype-based genetic test prediction score.[42] Of 1053 tested from 1997 to 2007, 359 patients (34%) were found to have a mutation in 1 or more HCM-associated genes on testing with polymerase chain reaction (PCR), high performance liquid chromatography, and direct DNA sequencing. Factors that were associated with a positive genetic test result in multivariate analyses were used to generate a predictive model to estimate the likelihood of a positive genetic test result, with each predictor assigned equipotent positive or negative weights. The most commonly identified variants were in MYBPC3 (n=96 [46%]), and MYH7 (n=74 [36%]). Compared with genotype-negative patients, genotype positive patients were younger at diagnosis (mean 36.4 years vs 48.5 years; p<0.001), had more hypertrophy (mean, 22.6 mm vs 20.1 mm; p<0.001), were more likely to have a family history of HCM (505 vs 23%; p<0.001), and were more likely to have a family history of SCD (27% vs 15%; p<0.001). Independent predictors of a positive genetic test were reverse curve HCM, age at diagnosis, maximum LV wall thickness, family history of HCM, family history of SCD, and presence of mild hypertension (negative association). When all 5 positive markers were present, the likelihood of a positive genetic test was 80%.

Marsiglia evaluated predictors of a positive genetic test among 268 index patients with clinically diagnosed HCM.[43] Pathogenic mutations were found in 131 subjects (48.8%), 79 (59.9%) in the MYH7 gene, 50 (38.2%) in the MYBPC3 gene, and 3 (2.3%) in the TNNT2 gene. Factors significantly associated with a positive genetic test in univariate models were entered into a multivariable regression model to predict the likelihood of a positive genetic test, which demonstrated that a family history of confirmed HCM, average heart frequency, history of nonsustained ventricular tachycardia, and age were significantly associated with genetic test results. The authors postulate that parameters from the multivariable model be used to predict genetic test results; however, the validity of the predictive equation was not evaluated in populations other than the derivation group.

Genotype-Phenotype Correlations

Given the variability in penetrance and expressivity in HCM-related gene mutations, a number of studies have evaluated the association between specific mutations and clinical features. Studies identified that evaluate the association between HCM-related phenotypes and the presence of *any* disease-causing mutation, compared with negative testing, or the presence of specific types of mutations, are described next.

A number of studies have focused specifically on mutations that lead to the presence or absence of sarcomere protein (SP). Lopes et al evaluated the effect of mutations leading to SP-related variants in a cohort of 874 individuals with HCM.[44] All subjects underwent evaluation with high throughput sequencing of genes associated with HCM, and 383 subjects were found to have mutations in the 8 SP genes most commonly associated with HCM (*MYH7, MYBPC3, TNNI3, TNNT2, MYL2, MYL3, ACTC1*, and *TPM1*). Patients with SP-related mutations tended to be younger, more likely to have a family history of HCM and SCD, more

likely to have asymmetric septal hypertrophy, had a greater maximum LV wall thickness, and had an increased incidence of SCD.

A study by van Velzen examined long-term outcomes in HCM patients with sarcomere mutations compared to HCM patients without any identified HCM mutations.[45] The study included 626 patients with HCM who received phenotyping and mutation testing between 1985 and 2014. Of these, pathogenic mutations were detected in 327 patients (52%). Patients with an HCM mutation were significantly younger and had more extreme hypertrophy than those without mutations. After 12 ± 9 years of follow-up, the presence of a mutation was associated with all-cause mortality (hazard ratio [HR] 1.90; 95% CI, 1.14 to 3.15; p = 0.014), cardiovascular mortality (HR 2.82, 95% CI, 1.49 to 5.36; p = 0.002), heart failure-related mortality (HR 6.33, 95% CI 1.79 to 22.41; p = 0.004), and sudden cardiac death/aborted sudden cardiac death (HR 2.88, 95% CI 1.23 to 6.71; p = 0.015).

In an evaluation of NGS testing of the *MYBPC3* gene in a cohort of 114 patients with clinically-defined HCM, Liu evaluated genotype-phenotype correlations.[46] Among the 20 patients with novel or known mutations detected, those with double mutations (n=2) or premature stop codon mutations (n=12) were more likely to have severe manifestations requiring invasive therapies (eg, septal myomectomy), compared with those with missense mutations (n=11). However, the small study population limits generalizability.

In a cohort of 137 patients with HCM diagnosed before age 21, 71 of whom (52%) were genotype positive, Loar found that those who were genotype positive had more cardiac hypertrophy and earlier myomectomies.[47] However, there were no differences in overall survival between genotype-positive and genotype-negative groups, and there were no significant differences in outcomes between the 2 major genotypes among genotype-positive subjects (i.e., those with *MYH7* and *MYBPC3* mutations).

Ellims evaluated cardiac fibrosis in 139 patients with HCM, 56 of whom underwent NGS for cardiomyopathy genes, using magnetic resonance imaging to evaluate regional myocardial fibrosis with late gadolinium enhancement (LGE) and diffuse myocardial fibrosis.[48] Among those who underwent NGS, 36 (64%) had a likely causative mutation detected, most commonly in the *MYBPC3* gene (n=17). Compared with genotype-negative patients, those with a causative mutation detected had more focal myocardial fibrosis (higher LGE; 7.9 vs 3.1, p=0.03), but less diffuse myocardial fibrosis (measured by post-contrast T_1 time: 498 vs 451, p=0.03).

Coppini reported differences in phenotype among patients with HCM (n=230) with mutations associated with thick-filament (n=150) or thin-filament (n=80) abnormalities.[49] Thin-filament mutations are generally less commonly identified than thick-filament mutations and include *TNNT2*, *TNNI3*, *TPN1*, and *ACTC*. Patients with thin-filament mutations were less likely to have dynamic outflow tract obstruction (19% vs 34% among those with thick-filament mutations, p=0.015).Over a mean follow up of 4.7 years, patients with thin-filament mutations were more likely to progress to stage III/IV heart failure than patients with thick-filament mutations (15% vs 5%, p=0.013) and were more likely to have LV ejection fraction under 50% (18% vs 8%, p=0.031) and a restrictive LV filling pattern (16% vs 5%, p=0.003).

A study by Page attempted to identify the disease expression and penetrance of *MYBPC3* mutations in a cohort of HCM patients and their relatives. Their findings support that clinical disease expression among carriers of HCM mutation is heterogeneous with mutation type (eg,

missense, nonsense) or specific mutation. In addition, demographic characteristics such as older patient age or male gender resulted in an increased disease penetrance.[50]

Multiple HCM Mutations

Multiple pathologic mutations are found in 1% to 10% of patients with HCM and are associated with more severe disease and a worse prognosis.[7,18,51] For these patients, targeted mutation analysis may miss additional HCM mutations. Some experts recommend comprehensive testing of all individuals for this reason; however, it is not known whether the presence of multiple pathologic mutations influences management decisions such that health outcomes might be improved.

Section Summary

In patients without a known familial HCM mutation, genetic testing provides little value in determining whether HCM will develop. For these patients, a negative gene test is not sufficient to rule out HCM and a positive genetic test is not sufficient for establishing the presence of clinical disease. Given that HCM is almost always inherited in an autosomal dominant fashion and is rarely spontaneous, genetic testing is most beneficial in families where there is an established clinical diagnosis of HCM and a known HCM mutation.

CLINICAL UTILITY

Predictive Testing: Mutation Detection in At-Risk Individuals

There are some benefits to predisposition genetic testing of at-risk individuals when there is a known mutation in the family. Inheritance of the predisposition to HCM can be ruled out with near certainty when the genetic test is negative (mutation not detected) in this circumstance. A positive test result (mutation detected) is less useful. It confirms the presence of a pathologic mutation and an inherited predisposition to HCM but does not establish the presence of the disease. It is possible that surveillance for HCM may be increased after a positive test, but the changes in management are not standardized.

Michels attempted to risk-stratify asymptomatic patients with a positive genetic test for HCM. The authors reported cardiac evaluation outcomes and risk stratification for SCD in 76 asymptomatic HCM mutation carriers identified from 32 families.[52] Between 2007 and 2008, 76 asymptomatic family members of 32 probands with HCM and known mutations were found to have mutations in 1 or more of the following genes: MYBPC3, MYH7, TNNT2, TNNI3, MYL2, MYL3, TPM1, ACTC, TNNC1, CSRP3, and TCAP. HCM was diagnosed in 31 (41%) asymptomatic family members. The authors attempted to risk stratify patients for SCD, and found that none of the screened carriers were symptomatic, had a history of syncope, or had severe hypertrophy (≥30 mm). Four carriers were found to have an abnormal blood pressure response during exercise, which is associated with worse prognosis; of those, three were diagnosed with HCM. Three carriers were found to have nonsustained ventricular tachycardia, which is also associated with worse prognosis in HCM; of those, two were diagnosed with HCM. The study does not have long enough follow-up to determine whether these risk factors were associated with differences in SCD rates.

A similar study by Alejandra Restrepo-Cordoba assessed whether genetic test results could be used to predict prognosis for HCM patients.[53] In this study, 100 patients with HCM were classified into either a poor or favorable prognosis group and were tested for pathogenic mutations. Mutations were identified in 28 patients from the poor prognosis group (56%) and

in 23 patients (46%) from the favorable prognosis group. Pathogenic mutations that had previously been associated with a poor prognosis were found in only five patients in the poor prognosis group. The authors concluded that "genetic findings are not useful to predict prognosis in most HCM patients. By contrast, real-world data reinforce the usefulness of genetic testing to provide genetic counselling and to enable cascade genetic screening.

A small study by McTaggart followed 14 asymptomatic individuals with pathogenic HCM mutations, seven of whom were children when they underwent genetic testing.[54] Three participants had a mutation in MYH7 and 11 had a mutation in MYBPC3. Ten were followed up for 18 years, one for 11 years, and one for 8 years. After follow-up, only one patient had developed phenotypic HCM by MRI and echocardiogram, and two others had features suggesting of HCM by MRI only.

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

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

Axelsson reported results of the INHERIT trial, a randomized, double-blind, placebo-controlled trial evaluating the use of losartan among 133 patients with HCM.[55] Patients with a diagnosis of HCM were eligible if they had unexplained LV hypertrophy with either a maximum wall thickness of 15 mm or more on echocardiography or borderline hypertrophy (maximum wall thickness 13-14 mm) and at least one first-degree relative with HCM. For the study's primary end point, change in LV mass at 12 months, there were no significant differences between the placebo and losartan groups (mean difference 1 g/m^2; 95% confidence interval, -3 to 6; p=0.60). In post hoc subgroup analyses based on genotype, there was no significant interaction between the treatment group and genotype.

Ho reported results of a small (n=38), double-blind, placebo-controlled pilot trial of the use of diltiazem in patients with a known sarcomere mutation (mutations in *MYBPC3*, *MYH7*, or *TNNT2*), but without septal hypertrophy.[56] The investigators analyzed *MYBPC3* and *MYH7* mutation carriers to assess for potential interaction between treatment and underlying genotype. In diltiazem-treated *MYBPC3* mutation carriers had significant decreases in LV wall thickness and mass, LV filling and cardiac troponin levels compared to *MYBPC3* mutation carriers treated with placebo. These beneficial changes were not observed in diltiazem-treated *MYH7* mutation carriers.

Carrier Testing: Mutation Detection for Reproductive Decision-Making

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

Section Summary

The use of genetic testing for HCM has the greatest utility in asymptomatic family members of patients with HCM who have a known genetic mutation. Given the high sensitivity of *known* mutations, the absence of a mutation in the asymptomatic relatives should rule out the presence of familial HCM and allow reduction in surveillance for complications. In other clinical scenarios, use of genetic testing for HCM has less clinical utility. Detection of mutations in asymptomatic carriers may aid reproduction decision making, although direct evidence is limited about the impact of genetic information in this setting.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY (ACC) FOUNDATION/AMERICAN HEART ASSOCIATION (AHA)[11]

In 2011, the ACC Foundation and the AHA issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy. The following recommendations were issued concerning genetic testing:

- Class I indications: Procedure/treatment should be performed/administered

  o Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM
  o 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
  o Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM
  o 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

- Class IIa indications: Additional studies with focused objectives are needed

  Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM

- Class IIb indications: Additional studies with broad objectives needed; additional registry data would be helpful.

  The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain

- Class III indications: No Benefit

  o Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation

- Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM

All ACC/AHA recommendations were given a Level B rating indicating limited populations were evaluated and the recommendation was based on a single randomized trial or nonrandomized studies.

HEART RHYTHM SOCIETY AND THE EUROPEAN HEART RHYTHM ASSOCIATION[57]

In 2011, the Heart Rhythm Society and the European Heart Rhythm Association (HRS/EHRA) published recommendations for genetic testing for cardiac channelopathies and cardiomyopathies based upon expert consensus. For hypertrophic cardiomyopathy, the following recommendations were made:

- Comprehensive or targeted (*MYBPC3, MYH7, TNNI3, TNNT2, TPM1*) 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.

SUMMARY

There is enough research to show that gene testing can be useful to guide treatment for individuals at risk for hypertrophic cardiomyopathy (HCM) that have a known HCM mutation in the family. Clinical guidelines based on research recommend testing for these specific mutations in family members at risk for HCM. Therefore, genetic testing may be considered medically necessary for first degree relatives of individuals with a known pathologic mutation.

For at-risk individuals who have a family member with HCM that has tested negative for pathologic mutations, genetic testing is considered not medically necessary because a positive mutation in an asymptomatic at-risk patient does not necessarily confer a diagnosis of HCM.

There is not enough research to show that genetic testing for HCM in other individuals, including people with a family history of HCM but no identified mutation, can improve treatment decisions or health outcomes. Therefore, genetic testing is considered investigational in patients where a familial HCM mutation is unknown.

REFERENCES

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CODES

Codes	Number	Description
CPT	81403	Tier 2 Molecular Pathology Procedures; Level 4
	81405	Tier 2 Molecular Pathology Procedures; Level 6
	81406	Tier 2 Molecular Pathology Procedures; Level 7
	81407	Tier 2 Molecular Pathology Procedures; Level 8
	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
HCPCS	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

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