Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) 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 mutation present in that affected relative to be eligible for coverage.

When Services Are Considered Not Medically Necessary
The use of genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) for patients with a family history of hypertrophic cardiomyopathy (HCM) in which a first-degree relative with established HCM has tested negative for pathologic mutations is considered to be not medically necessary.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) 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 to be investigational.*

Background/Overview
Familial HCM is an inherited condition that is caused by a mutation in 1 or more of the cardiac sarcomere genes. Hypertrophic cardiomyopathy is associated with numerous cardiac abnormalities, the most serious of which is sudden cardiac death (SCD). Genetic testing for HCM-associated mutations is currently available through a number of commercial laboratories.

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

The genetic basis for HCM is a defect in the cardiac sarcomere, which is the basic contractile unit of cardiac myocytes and is composed of a number of different protein structures. Nearly 1400 individual mutations in...
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at least 18 different genes have been identified to date. Approximately 90% of pathogenic mutations 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). 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. In patients with clinically documented HCM, genetic abnormalities can be identified in approximately 60%. Most patients with clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo mutations.

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. 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. 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 mutation is present, including among affected family members. This variability in clinical expression may be related to environmental factors and modifier genes. A large percentage of patients with HCM, perhaps the majority of all HCM patients, are asymptomatic or have minimal symptoms. These patients do not require treatment and are not generally at high risk for SCD. A subset of patients has severe disease that causes a major impact on quality of life and life expectancy. Severe disease can lead to disabling symptoms, as well as complications of HCM, including heart failure and malignant ventricular arrhythmias. Symptoms and presentation may include SCD due to unpredictable ventricular tachyarrhythmias, heart failure, or atrial fibrillation, or some combination. 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.

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 3 to 5 years for adults. Additional screening is recommended for any change in symptoms that might indicate the development of HCM.
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Genetic Testing for Familial Hypertrophic Cardiomyopathy

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 family member with established HCM. Results of genetic testing may influence 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.

Commercial testing has been available since May 2003, and there are numerous commercial companies that currently offer genetic testing for HCM. 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 9 and 52. Additional testing characteristics of some of the commercially available panels are presented in Table 1. 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. With next generation and whole-exome sequencing techniques, the sensitivity of identifying variants on the specified genes has increased substantially. At the same time, the number of variants of unknown significance is also increased with next generation sequencing (NGS). Also, the percent of individuals who have more than 1 mutation that is thought to be pathogenic is increasing. A study in 2013 reported that 9.5% (19/200) patients from China with HCM had multiple pathogenic mutations and that the number of mutations correlated with severity of disease.

Table 1. Characteristics of Commercial Testing for HCM

<table>
<thead>
<tr>
<th>Company</th>
<th>No. of HCM Genes in Panel</th>
<th>Testing Technique</th>
<th>Turnaround Time, wk</th>
<th>No. of Probability Categories</th>
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</thead>
<tbody>
<tr>
<td>GeneDx® (Gaithersburg, MD)</td>
<td>18</td>
<td>NGS and deletion/duplication analysis</td>
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<td>5</td>
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<tr>
<td>Transgenic (Omaha, NE)</td>
<td>12</td>
<td>Direct (Sanger) sequencing</td>
<td>2-4 (targeted)</td>
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<td></td>
<td></td>
<td></td>
<td>4-6 (comprehensive)</td>
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<td>Partners (Cambridge, MA)</td>
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<td>NGS and Sanger sequencing</td>
<td>5</td>
<td>5</td>
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<td>NGS</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Prevention Genetics (Marshfield, WI)</td>
<td>15</td>
<td>NGS, Sanger sequencing, and/or deletion/duplication analysis</td>
<td>5-7</td>
<td>4</td>
</tr>
<tr>
<td>Invitae (San Francisco, CA)</td>
<td>52</td>
<td>NGS and deletion/duplication/CNV analysis</td>
<td>2-3</td>
<td>NS</td>
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</tbody>
</table>

Adapted from Maron et al and GeneTests.org.
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Some of these panels include testing for multisystem storage diseases that may include cardiac hypertrophy, such as Fabry disease (GLA), familial transthyretin amyloidosis (TTR), X-linked Danon disease (LAMP2). Several academic centers, including Emory University School of Medicine and Washington University in St. Louis, also offer HCM genetic panels.

Other panels include testing for genes that are related to HCM but also those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen, Irvine, CA) is an NGS panel of 44 genes that are 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.

CNV: copy number variant; HCM: hypertrophic cardiomyopathy; NGS: next-generation sequencing

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 HCM are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

The rationale for this policy statement is based primarily on a 2010 technology evaluation center (TEC) Assessment that considered whether genetic testing for patients at risk for HCM improves outcomes. This Assessment reviewed the evidence on the accuracy of genetic testing in identifying patients who will subsequently develop HCM. Seven studies were identified that met the inclusion criteria for review. These peer-reviewed articles were supplemented by data on analytic validity available through the manufacturers' websites or personal communication.

Analytic and Clinical Validity

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. 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.

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.

Multiple pathologic mutations are found in 1% to 10% of patients with HCM and are associated with more severe disease and a worse prognosis. For these patients, targeted mutation analysis may miss mutations other than the one tested for. 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.

Clinical Validity
The clinical validity of genetic testing for HCM is considerably lower than the analytic validity. Evidence on clinical sensitivity, (probability that a person with 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 mutation detection rate ranges from 33% to 67%. The less-than-perfect mutation detection rate is due in part to the published studies having investigated some, but not all, of the known genes that underlie HCM, and investigators in these studies using mutation scanning methods such as single-strand conformation polymorphism or denaturing gradient gel electrophoresis that will miss certain deleterious mutations. Another reason for the less-than-perfect mutation detection rate is that other, as yet unidentified, genes may be responsible for HCM. Finally, there may be unknown, nongenetic factors that mimic HCM. Mutation detection rates will likely increase over time with recognition of new mutations.

Given the large size of many of the genes associated with HCM, particularly MYBPC3 and MYH7, the use of NGS methods has been investigated as a more efficient way to evaluate for genetic mutations in HCM. Next generation sequencing refers to 1 of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. The use of NGS and whole-exome sequencing has the potential to substantially increase the sensitivity of genetic testing for HCM. Small studies have demonstrated the
potential role of NGS in detecting recognized and novel mutations. Gomez et al reported the yield of a 2-step NGS process in a cohort of 136 patients with clinically diagnosed HCM. In a validation cohort of 60 patients with both NGS results and prior identification of a mutation in MYH7, MYBPC3, TNNT2, TNNT3, 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 et al developed an NGS platform to evaluate the most common genetic mutations in a cohort of 75 patients with HCM and dilated cardiomyopathy. The authors report very high analytic sensitivity (98.9%) for previously-detected mutations in the covered regions.

Predictors of Mutation Detection

Several studies that evaluated clinical predictors of detecting a mutation have been published.

A study by Ingles et al included 265 unrelated individuals with HCM, in which a total of 52% (138/265) had a mutation identified. 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 SCD (89% vs 59%, p<0.001). Other predictors of finding a pathogenic mutation were female gender and increased left ventricular (LV) wall thickness.

A second study by Gruner et al derived a score for predicting the likelihood of finding a mutation, called the Toronto Hypertrophic Cardiomyopathy Genotype Score. 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.

Bos et al conducted a retrospective evaluation of 1053 patients with a clinical diagnosis of HCM and available HCM genetic testing for 9 HCM-associated myofilament genes to develop a phenotype-based genetic test prediction score. 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 et al evaluated predictors of a positive genetic test among 268 index patients with clinically-diagnosed HCM. Pathogenic mutations were found in 131 subjects (48.8%), 79 (59.9%) in the MYH7 gene,
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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. 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.

In an evaluation of NGS testing of the MYBPC3 gene in a cohort of 114 patients with clinically-defined HCM, Liu et al evaluated genotype-phenotype correlations. 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 et al found that those who were genotype positive had more cardiac hypertrophy and earlier myomectomies. 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 (ie, those with MYH7 and MYBPC3 mutations).

Ellims et al 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. 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 T1 time: 498 vs 451, p=0.03).
Coppini et al reported differences in phenotype among patients with HCM (n=230) with mutations associated with thick-filament (n=150) or thin-filament (n=80) abnormalities. 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 et al 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.

Clinical Implications of Test Characteristics
Because of the imperfect clinical sensitivity, a negative test is not sufficient to rule out HCM in patients without a known mutation in the family. A positive genetic test in a patient without a known family history of disease increases the likelihood that an individual carries a pathologic mutation but is not sufficient for establishing the presence of clinical disease.

A positive genetic test result does not indicate that the individual has clinical HCM. The other important component to clinical validity in this context is penetrance, or the probability that an individual with a pathogenic mutation will eventually develop the condition of concern. There is reduced penetrance in HCM (ie, not everyone with a deleterious mutation will develop manifestations of HCM). In addition, penetrance varies among different mutations and may even vary among different families with an identical pathologic mutation. As a result, it is not possible to estimate accurately the penetrance for any given mutation in a specific family.

Section Summary: Analytic and Clinical Validity
The available evidence on testing for mutations related to HCM indicates a high analytic sensitivity and specificity. This indicates that in cases where there is interest in identifying a specific mutation (ie, when there is a known mutation in an affected family member), testing can rule in or rule out the presence of a mutation with high certainty. In contrast, given the wide genetic variation in HCM and the likelihood that not all causative mutations have been identified, there is imperfect clinical sensitivity. Therefore, a negative test is not sufficient to rule out a mutation in patients without a known family mutation. 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. A number of studies have investigated models for predicting a positive genetic test among patients with clinical HCM, but the clinical use of these models is not well established. The available evidence has not demonstrated that specific genetic testing results are associated with HCM-related phenotype or disease penetrance.
Clinical Utility
Genetic testing for HCM may potentially play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals; genetic testing for diagnosis or prognosis in patients with HCM; and genetic testing for reproductive decision making.

Predictive Testing: Mutation Detection in At-Risk Individuals
There are benefits to predisposition genetic testing for 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, and it is also possible that surveillance will be essentially the same following a positive test.

Michels et al 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. 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. Hypertrophic cardiomyopathy 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, 3 were diagnosed with HCM. Three carriers were found to have nonsustained ventricular tachycardia, which is also associated with worse prognosis in HCM; of those, 2 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.

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 (eg, 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.

If a familial mutation is not known and an at-risk individual undergoes testing, a positive result (mutation detected) would confirm an inherited predisposition to HCM and an increased risk for clinical manifestations in the future. However, a negative result (no mutation detected) could not exclude the possibility that a mutation was inherited. In this case, risk assessment and surveillance for HCM would depend on the family
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History and other personal risk factors. Thus, in this situation, testing has limited utility in decision making. Moreover, if a familial mutation is not known, comprehensive mutation analysis would be the method of choice, and in addition to a positive or negative result, there is the possibility of detecting a variant of uncertain significance—a variant for which the association with clinical disease is not known.

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 et al reported results of the INHERIT trial, a randomized, double-blind, placebo-controlled trial evaluating the use of losartan among 133 patients with HCM. 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/m²; 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 et al 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. Over 2 years of follow up, patients in the diltiazem group (n=18) had improvement in mean left ventricular end-diastolic diameter (LVEDD), while controls (n=20) had decreased LVEDD (change in z score, 0.5 vs -0.5, p<0.001). The mean LV thickness-to-dimension ratio was stable in the diltiazem group but worsened in controls (-0.02 vs 0.15, p=0.04).

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.

Additionally, rudimentary disease prevention based on assisted reproduction using preimplantation genetic diagnosis (PGD) is possible. PGD uses in vitro fertilization with a single cell removed from early-stage embryos and tested for the familial mutation. Only those embryos without the identified HCM mutation are used to initiate pregnancy. Disease-modifying studies are in development using animal models of HCM. In rodent models, sarcomere mutations have been implicated in early abnormal intracellular calcium handling far in advance of LVH. Treatment of this calcium handling by use of diltiazem appeared to attenuate the development of LVH when started in early life. The feasibility of this strategy in humans is being assessed by an ongoing randomized controlled trial (NCT00319982), which compares diltiazem to placebo in known sarcomere mutation carriers who have yet to develop LVH; this study has completed enrollment, but has not reported results.
Section Summary
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 for 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 reproductive decision making, although direct evidence is limited about the impact of genetic information in this setting.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
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NCT: national clinical trial.

Clinical Input Received 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.

Clinical input was solicited in January 2011 on general agreement with the policy. This was followed up by a second round of focused clinical vetting in October 2011 to address specific questions raised after the first round of vetting. The initial vetting indicated uniform agreement with the medically necessary indication for individuals with a first-degree relative who has a known pathologic mutation. This vetting also asked whether testing should be restricted to first-degree relatives. For this question, there was a mixed response, with 2 reviewers indicating that they agree with testing only first-degree relatives, two reviewers indicating that testing should be offered to non-first-degree relatives, and 1 reviewer who was unsure.

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

The evidence for testing for specific HCM-related mutation identified in affected family member(s) in individuals who are asymptomatic with risk for HCM because of a positive family history includes studies reporting on the analytic and clinical validity of testing. Relevant outcomes include 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 mutation in the family. In this situation, genetic testing will establish the presence or absence of the same mutation in a close relative with a high degree of certainty. Absence of this mutation 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. These patients 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 indirect chain of evidence that there are management changes that improve outcomes with genetic testing when there is a known familial mutation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for nonspecific testing for HCM-related mutation(s) in individuals who are asymptomatic with risk for HCM because of a positive family history includes studies reporting on the analytic and clinical validity of testing. Relevant outcomes include 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 mutations have been identified, there is imperfect clinical sensitivity. Therefore, a negative test is not sufficient to rule out a mutation in patients without a known family mutation. On the other hand, variability in clinical penetrance means that a positive genetic test does not always “rule in” clinical HCM. For at-risk individuals without a known mutation in the family, the evidence does not permit conclusions of the effect of genetic testing on outcomes, since there is not a clear relationship between testing and improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
Current Effective Date: 03/15/2017


15. Correlagan Personal Communication. 4/27/2010

16. PGxHealth Personal Communication. 4/22/2010


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53. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011;8(8):1308-1339. PMID 21787999

Policy History

Original Effective Date: 04/25/2012
Current Effective Date: 03/15/2017

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02/15/2006 Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
02/23/2006 Quality Care Advisory Council approval
02/13/2008 Medical Director review
02/20/2008 Medical Policy Committee approval. No change to coverage eligibility.
02/04/2009 Medical Director review
02/19/2009 Medical Policy Committee approval. No change to coverage eligibility.
02/04/2010 Medical Director review
02/17/2010 Medical Policy Committee approval. Title changed to Extracorporeal Shock Wave Treatment for Plantar Fasciitis and Other Musculoskeletal Conditions.
02/03/2011 Medical Policy Committee review
02/16/2011 Medical Policy Implementation Committee approval. No change to coverage statement.
02/02/2012 Medical Policy Committee review
02/15/2012 Medical Policy Implementation Committee approval. No change to coverage statement.
01/03/2013 Medical Policy Committee review
01/09/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013 Coding revised
01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2015 Medical Policy Committee review
03/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/03/2016 Medical Policy Committee review
03/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
03/02/2017 Medical Policy Committee review
03/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 3/2018

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<tr>
<td>CPT</td>
<td>81403, 81405, 81406, 81407, 81479</td>
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<td>HCPCS</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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