Title: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

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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 (SCD). Genetic testing for HCM-associated mutations is currently available through a number of commercial laboratories.

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 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 composed of a number of different protein structures. (5) Nearly 1,400 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**, **TNNT3**, **TNNT1**, **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) In patients with clinically documented HCM, genetic abnormalities can be identified in approximately 60%. (7, 9) Most patients with clinically documented disease are demonstrated to have a familial pattern, 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 (MRI), 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’s syndrome and Friederich’s 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.

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 12-18 months for individuals between the ages of 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 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.

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 the FDA has technical authority to regulate home-brew tests, there is currently no active oversight nor 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.

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 mutation present in that affected relative. (See Policy Guidelines section)

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 has tested negative for pathologic mutations.

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.

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 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. In order to inform and direct genetic testing for at-risk individuals, genetic testing should be initially performed in at least one close relative with definite HCM (index case), if possible.
3. Because there are varying degrees of penetrance for different HCM mutations, 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.

RATIONALE
Commercial testing has been available since May 2003, and there are numerous commercial companies that currently offer genetic testing for hypertrophic cardiomyopathy (HCM). (6, 11-14) 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 genes, and additional testing characteristics are presented in Table 1. (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.

Table 1. Characteristics of Commercial Testing for HCM

<table>
<thead>
<tr>
<th>Company</th>
<th>Began HCM Testing (Year)</th>
<th>Number of HCM Genes in Panel</th>
<th>Turnaround Time (Weeks)</th>
<th>No of Probability Categories</th>
</tr>
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<tbody>
<tr>
<td>GeneDX (Gaithersburg, Maryland)</td>
<td>2008</td>
<td>18</td>
<td>8</td>
<td>5</td>
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<tr>
<td>Transgenomic-FAMILION</td>
<td>2008</td>
<td>12</td>
<td>4-6</td>
<td>3</td>
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<tr>
<td>Correlagen Diagnostics (Waltham, Massachusetts)</td>
<td>2007</td>
<td>16</td>
<td>6-8</td>
<td>7</td>
</tr>
<tr>
<td>Partners (Cambridge, Massachusetts)</td>
<td>2003</td>
<td>18</td>
<td>5</td>
<td>5</td>
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</table>

Adapted from Maron et al. (6)
The rationale for this policy statement is based primarily on a 2009 TEC Assessment (15) 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. (16-22) These peer-reviewed articles were supplemented by data on analytic validity available through the manufacturers’ websites or personal communication. (11-14, 23)

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.

The analytic sensitivity (ability to 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. (23) There are scant data available on the analytic specificity 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. (18, 22) However, the rate of false-positive results is likely to be higher for classification of previously unknown variants.

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 1-5% of patients with HCM and are associated with more severe disease and a worse prognosis. (7) 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, the number of patients with multiple pathologic mutations that will be missed through targeted testing is small.

However, 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 (i.e., not everyone with a deleterious mutation will develop manifestations of HCM). (24) In addition, penetrance varies among different mutations and may even vary among different families with an identical pathologic mutation. (25) As a result, it is not possible to estimate accurately the penetrance for any given mutation in a specific family.

A study by Page and colleagues 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 heterogenous with mutation type (e.g., missense, nonsense, etc.) or specific mutation. In addition, demographic characteristics such as older patient age or male gender resulted in an increased disease penetrance. (26)
The clinical validity of genetic testing for HCM is considerably lower than the analytic validity. Evidence on clinical sensitivity, also called the mutation detection rate, consists of several case series of patients with established HCM. To date, the published mutation detection rate ranges from 33–63%. (16-17, 19-21) 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 (SSCP) or denaturing gradient gel electrophoresis (DGGE) that will miss certain deleterious mutations. Presumably more comprehensive mutation analysis methods (e.g., sequence analysis with or without deletion duplication analysis) could identify additional 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.

Therefore, for patients without a known mutation in the family, a negative test is not sufficient to rule out HCM because of the suboptimal clinical sensitivity. 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.

Clinical Utility. 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.

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.

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 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.

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. A clinical trial affiliated with University of Pittsburgh (NCT00156429) is currently recruiting patients with HCM to assess genetic predictors of clinical outcomes. Targeted enrollment is 540 participants with an expected completion date of May 2020.

Additionally, rudimentary disease prevention based on assisted reproduction using preimplantation genetic diagnosis (PGD) is possible. PGD utilizes 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 left ventricular hypertrophy (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. (27)

Clinical Input Received through 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 in order 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 two 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 one 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 one 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. (10)

Summary
For individuals at risk for hypertrophic cardiomyopathy (HCM) (first-degree relatives), genetic testing is most useful when there is a known mutation in the family. In this situation, genetic
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. Therefore, genetic testing may be considered medically necessary for first-degree relatives of individuals with a known pathologic mutation.

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. Genetic testing is considered investigational for this purpose. For at-risk individuals who have a family member with HCM who tests negative for pathologic mutations, genetic testing is not indicated. Genetic testing is considered not medically necessary in this situation.

**Clinical Guidelines and Position Statements**

The ACC Foundation and the AHA issued joint guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy in 2011. (28) The following recommendations were issued concerning genetic testing:

**Class I indications**
- Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM (*Level of Evidence: 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 (*Level of Evidence: B*)
- Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM (*Level of Evidence: 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 (*Level of Evidence: B*)

**Class IIa indications**
- Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM (*Level of Evidence: B*)

**Class IIb indications**
- The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain (*Level of Evidence: B*)

**Class III indications: No Benefit**
- Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation (*Level of Evidence: B*)
- Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM (*Level of Evidence: B*)
- The Heart Rhythm Society and the European Heart Rhythm Association published recommendations for genetic testing for cardiac channelopathies and cardiomyopathies in 2011. (29) For hypertrophic cardiomyopathy, the following recommendations 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.

**CODING**

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<td>81405</td>
<td>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</td>
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<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>S3865</td>
<td>Comprehensive gene sequence analysis for hypertrophic cardiomyopathy</td>
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<td>S3866</td>
<td>Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family</td>
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• Effective in 2013, there are CPT codes that can be used to report this testing.
  • Code 81405 includes:
    ▪ ACTC1 (actin, alpha, cardiac muscle 1) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
    ▪ MYL2 (myosin, light chain 2, regulatory, cardiac, slow) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
    ▪ MYL3 (myosin, light chain 3, alkali, ventricular, skeletal, slow) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
    ▪ TNNI3 (troponin I, type 3 [cardiac]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
    ▪ TPM1 (tropomyosin 1 [alpha]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
  • Code 81406 includes:
    ▪ TNNT2 (troponin T, type 2 [cardiac]) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
• Code 81407 includes:
  ▪ MYBPC3 (myosin binding protein C, cardiac) (e.g., familial hypertrophic cardiomyopathy), full gene sequence
  ▪ MYH7 (myosin, heavy chain 7, cardiac muscle, beta) (e.g., familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence
• Code 81479 (unlisted molecular pathology procedure) would be used to report TNNC1, ACTN2 and MYOZ2 testing.
• Prior to 2013, there was no specific CPT code for this type of testing. Multiple codes that describe genetic analysis would likely have been used (e.g., 83890-83912). An example of coding for this testing in a new patient from one laboratory found on the internet included 83891x1, 83900x1, 83901x51, 83904x51, 83909x3 and 83912x1.
• There are specific HCPCS “S” codes for this testing: S3865 and S3866

**ICD-9 Diagnoses**

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<td>V17.41</td>
<td>Family history of sudden cardiac death [SCD]</td>
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<td>V17.49</td>
<td>Family history of other cardiovascular diseases</td>
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<td>V82.719</td>
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<td>V82.79</td>
<td>Other genetic screening</td>
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**ICD-10 Diagnoses (Effective October 1, 2014)**

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<td>I42.2</td>
<td>Other hypertrophic cardiomyopathy</td>
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<td>I42.8</td>
<td>Other cardiomyopathies</td>
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<tr>
<td>Z82.41</td>
<td>Family history of sudden cardiac death</td>
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<td>Z82.49</td>
<td>Family history of ischemic heart disease and other diseases of the circulatory system</td>
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**REVISIONS**

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<td></td>
<td>▪ ICD-10 Diagnoses added</td>
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REFERENCES
29. 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 2011; 8(8):1308-39.