The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is required; the ordering/requesting physician should submit documentation to Use Management.* Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**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.

Familial hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately one 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 1,000 individual mutations in at least 14 different genes have been identified to date. (6, 7) 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%. (6, 8) Most patients with clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo mutations. (8)

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. (6) 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. (8) 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. (9) A large percentage of patients with HCM, perhaps the majority of all HCM patients, are asymptomatic or have minimal symptoms. (8, 9) 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 three to five years for adults. (9) Additional screening is recommended for any change in symptoms that might indicate the development of HCM. (9)

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.

Related Protocol:

Genetic Testing for Inherited Disorders

Corporate Medical Guideline

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)

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.

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.

Policy Guideline

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.
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. See Benefit Application section for information regarding testing of the index case.

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.

**Benefit Application**

Recommendations indicate that, when possible, genetic testing for hypertrophic cardiomyopathy (HCM) be performed in an affected family member so that testing in unaffected, at-risk family members can focus on the mutation found in the affected family member. This testing is intended to document whether a known pathologic mutation is present in the family, and optimize the predictive value of predisposition testing for at-risk relatives.

See also Protocol Genetic Testing for Inherited Disorders.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


13. PGxHealth® Personal Communication 2010.


26. 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.