Corporate Medical Policy

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy AHS – M2086

File Name: genetic_testing_for_predisposition_to_inherited_hypertrophic_cardiomyopathy
Origination: 01/01/2019
Last CAP Review: N/A
Next CAP Review: 01/01/2020
Last Review: 05/01/2019

Description of Procedure or Service

Hypertrophic cardiomyopathy (HCM) is a commonly inherited cardiovascular disease defined as thickening of the ventricular wall resulting from more than 1500 mutations in 11 or more genes encoding proteins of the cardiac sarcomere (M.Marom, 2018b).

Related Policies
Genetic Testing for Dilated Cardiomyopathy AHS – M2073
Genetic Testing for Cardiac Ion Channelopathies AHS – M2025
ST2 Assay for Chronic Heart Failure AHS – G2130

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for predisposition to inherited hypertrophic cardiomyopathy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy is covered

Genetic Counseling is considered medically necessary and recommended for genetic testing of familial hypertrophic cardiomyopathy.

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered medically necessary for patients who meet the diagnostic criteria for HCM in order to facilitate cascade screening of their first-degree relatives.

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered medically necessary for individuals who are at risk for development of HCM, defined as having a
Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy AHS – M2086

first-degree relative with established HCM, when there is a known pathogenic gene mutation present in that affected relative.

When Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy is not covered

Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with HCM 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 Guidelines

Background
HCM is characterized by left ventricular hypertrophy (LVH, thickness of ≥15 mm), observed by echocardiography or magnetic resonance imaging and not otherwise explainable by other cardiovascular issues, such as coronary artery disease, hypertension, valvular disease, and congenital heart disease. Development of LVH usually starts in adolescence and is complete by early adulthood. Symptoms include chest pain, dyspnea and syncope, and severe disease can lead to disabling complications, including heart failure and malignant ventricular arrhythmias. However, many patients with HCM are asymptomatic or have minimal symptoms and are only discovered through means such as family screenings or an abnormal ECG (M. Maron, 2018a). HCM is the most frequent cause of sudden death in young people and can lead to functional disability from heart failure and stroke (B. J. Maron, 2003). HCM is a relatively common finding with a prevalence of approximately 1 in 500 people (B. J. Maron et al., 1995). However, estimates of clinically expressed HCM plus gene carriers are as high as 1 in 200 (Semsarian, Ingles, Maron, & Maron, 2015).

More than 90% of HCM is inherited as an autosomal-dominant disease with variable expressivity and age-related penetrance (Frustaci et al., 2018). Currently, relevant genetic abnormalities can be detected in approximately 60 percent of patients with clinically documented HCM (A. L. Cirino et al., 2017; B. J. Maron, Maron, & Semsarian, 2012). Most of the genetic mutations associated with HCM are found in the genes encoding various proteins that make up the cardiac sarcomere, the basic contractile unit of cardiac myocytes. More than 1500 pathogenic variants have been identified in at least 11 different genes (A. L. Cirino, Ho, Carolyn, 2014; B. J. Maron et al., 2012). Mutations in myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) are the most common and account for roughly 70 percent of HCM. Other genes implicated in HCM are regulatory myosin light chain (MYL2) and cardiac troponin T (TNNT2). Non-sarcomeric genes encoding plasma membrane or mitochondrial proteins, or Z-disc encoding genes, have also been documented (Frustaci et al., 2018).

Wide phenotypic variability exists, ranging from asymptomatic to severe life-threatening heart failure even within the same mutation. This variability in clinical expression may be related to environmental factors and modifier genes (Alcalai, Seidman, & Seidman, 2008). Moreover, there is not a strong correlation between left ventricular problems and symptoms; patients with major obstructions or hypertrophy may be asymptomatic and vice versa (M. Maron, 2018a). The primary characteristic of LVH is present in multiple conditions such as systemic hypertension, Fabry disease, aortic stenosis, and more. Such conditions should be excluded before a diagnosis of HCM is made (M. Maron, 2018a).
Diagnostic screening of first-degree relatives is important to identify at risk patients. Guidelines have been established for clinically unaffected relatives of affected individuals. Clinical 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 with additional screening recommended for any change in symptoms (Gersh et al., 2011).

**Clinical Utility and Validity**

A recent study by Cirino et al compared the results from panel genetic testing to whole genome sequencing (WGS). Forty-one patients with HCM who had undergone targeted genetic testing (either multigene panel or familial variant test) were recruited into a clinical trial of WGS. Panel size ranged from 4-62 genes, and all but 2 subjects were tested for the main 8 sarcomeric genes. The authors stated that WGS detected nearly all variants identified on panel testing and allowed further analysis of posited disease genes. Several variants of uncertain clinical use and other genetic findings were also identified. Panel testing and WGS provided similar results, but WGS requires reanalysis over time; however, WGS also requires genomic expertise to correctly interpret results (A. L. Cirino et al., 2017).

A study focusing on the non-sarcomeric genes contributing to HCM was performed by Walsh et al. A reference sample of 60,706 exomes were analyzed and compared to 6,179 HCM cases. This comparison revealed a large amount of gene variants in the main eight sarcomeric genes (MYH7, MYBPC3, TNN12, TPM1, MYI2, MYL3, TNNI3, ACTC1) but very few variants of the non-sarcomeric genes in HCM cases. The authors concluded the variation in most of the non-sarcomeric genes does not affect HCM significantly as 99% of HCM pathogenic variants were found to be in the main eight sarcomeric genes. Four non-sarcomeric genes were found to have an excess of variants, but even these amounted to only 2% of the HCM cases overall; the other 26 non-sarcomeric genes examined were found to have very little or no excess variation over the reference sample of exomes. Furthermore, the authors state that only the well-known variants are symptomatic whereas the other variants are of unknown significance or benign, making clinical sequencing of limited use. The authors recommended that the only genes tested should be the eight sarcomeric genes, the metabolic cardiomyopathy genes, and possibly ACTN2 and MYOZ2 (Walsh et al., 2017).

**Applicable Federal Regulations**

A search on the FDA website on December 12, 2018, found zero results regarding any FDA-approved genetic testing for hypertrophic cardiomyopathy. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Guidelines and Recommendations**

**American College of Cardiology Foundation (AACC)/American Heart Association (AHA) (2011)**

Evaluation of inheritance and genetic counseling are recommended for HCM patients. Ideally, the counseling would be provided by a specialist knowledgeable in the genetics of cardiovascular disease. Screening of first-degree relatives of an HCM patient and genetic testing for any atypical forms of HCM are also recommended. Genetic testing to identify first degree family members at risk for HCM is also deemed “reasonable”.
Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy AHS – M2086

Routine clinical screening and genetic testing for relatives were not recommended for a genotype-negative patient. Genetic testing for assessing SCD risk in HCM was also of unknown utility. (Gersh et al., 2011)

**European Society of Cardiology (ECS, 2014)**
Genetic counselling is recommended for all HCM patients when the HCM is not explained solely by a non-genetic cause.

Genetic testing is recommended for patients fulfilling the diagnostic criteria for HCM, both as a confirmatory test and to enable genetic testing for relatives. Both cascade genetic screening and a clinical evaluation are recommended for first-degree relatives that carry the same mutation as the HCM patient (“proband”). Even if a mutation is absent, relatives should consider reassessment should symptoms appear or other clinical data emerges. A genetic analysis, such as pedigree analysis and high-throughput sequencing, should include the most commonly implicated sarcomere protein genes. If a rarer condition is suspected, the analysis should include the gene responsible for that condition.

Pre-natal genetic testing is not recommended due to phenotypic variability (Elliott et al., 2014).

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force has not addressed genetic testing for hypertrophic cardiomyopathy.

### Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

**Applicable service codes: 81403, 81405, 81406, 81407, 81439, 81479, 96040, S0265, S3865, S3866**

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy AHS – M2086

Scientific Background and Reference Sources


Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy AHS – M2086


**Policy Implementation/Update Information**

1/1/2019  New policy developed. BCBSNC will provide coverage for genetic testing for predisposition to inherited hypertrophic cardiomyopathy when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

5/14/19  Reviewed by Avalon 1st Quarter 2019 CAB. Related Policies section added. Moved the following statement from the When Not Covered to the When Covered section of the policy: “Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered medically necessary for patients who meet the diagnostic criteria for HCM in order to facilitate cascade screening of their first-degree relatives.” Policy guidelines extensively updated, along with references. Billing/Coding section updated to align with policy. Medical Director review 5/2019. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.