MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR PREDISPOSITION TO INHERITED HYPERTROPHIC CARDIOMYOPATHY
POLICY NUMBER	MP 2.248

Effective Date:	12/1/2023

I. POLICY

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 variant 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 with established hypertrophic cardiomyopathy has tested negative for pathologic variants.

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. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

Due to the complexity of genetic testing for hypertrophic cardiomyopathy (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 HCM.

To inform and direct genetic testing for at-risk individuals, genetic testing should initially be performed in at least one (1) close relative with definite HCM (index case), if possible.

Because there are varying degrees of penetrance for different HCM variants, 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.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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Familial Hypertrophic Cardiomyopathy

Familial hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular condition, with a phenotypic prevalence of approximately 1 (0.2%) in 500 adults. It is the most common cause of sudden cardiac death (SCD) in adults younger than 35 years of age and is probably the most common cause of death in young athletes. The overall mortality 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 different protein structures. Around 1400 disease-associated variants in at least 18 different genes have been identified. About 90% of pathogenic variants 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*). Variants 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 the clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants.

Diagnosis and Management

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy, measured by echocardiography or magnetic resonance imaging, in the absence of other known causative factors such as valvular disease, long-standing hypertension, or another myocardial disease. In addition to primary cardiac disorders, there are systemic diseases that can lead to left ventricular hypertrophy and thus mimic HCM. They include infiltrative diseases such as amyloidosis, glycogen storage diseases (e.g., Fabry disease, Pompe disease), and neuromuscular disorders (e.g., Noonan syndrome, 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 variant 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, 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. Implantable cardioverter defibrillator implantation may be indicated if there is a family history of SCD.

Diagnostic screening of first-degree relatives and other family members is an important component of HCM management. Guidelines have been established for screening clinically unaffected relatives of affected individuals. Screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals ages 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.

Genetic Testing

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 relative with established HCM. Results of genetic testing may influence the 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. However, the likelihood of obtaining a positive genetic test in the proband is only about 50% because all genes causing HCM have not yet been identified or are absent from testing panels. Failure to identify the causative variant in the proband is an indeterminate result that provides no useful information and precludes predictive testing in 33% to 67% of cases.

Commercial testing has been available since 2003, and numerous companies offer genetic testing for HCM. Testing is performed either as a comprehensive or targeted gene test. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes most commonly associated with genetic variants for HCM and evaluates whether any potentially pathogenic variants are present. Some available panels include testing for multisystem storage diseases that may include cardiac hypertrophy, such as Fabry disease (*GLA*), familial transthyretin amyloidosis (*TTR*), and X-linked Danon disease (*LAMP2*).

Other panels include testing for genes related to hypertrophic cardiomyopathy and those associated with other cardiac disorders. For example, the Pan Cardiomyopathy panel (Laboratory for MolecularMedicine) is a next-generation sequencing panel of 62 genes associated with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, left

ventricular noncompaction syndrome, Danon syndrome, Fabry disease, Brugada syndrome, and transthyretin amyloidosis.

For a patient with a known variant in the family, targeted testing is performed. Targeted variant testing evaluates for the presence or absence of a single variant known to exist in a close relative.

It can be difficult to determine 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 sequencing 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 uncertain significance is also increased with next-generation sequencing. Also, the percentage of individuals who have more than 1 variant that is thought to be pathogenic is increasing. A 2013 study reported that 9.5% (19/200) patients from China with HCM had multiple pathogenic variants and that the number of variants correlated with severity of disease.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Sequencing tests for HCM are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

No assay kits have been approved by the Food and Drug Administration for genetic testing for HCM.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who are asymptomatic with risk for HCM because of a positive family history who receive testing for a specific HCM-related variant identified in affected family member(s), the evidence includes studies reporting on the clinical validity of testing. Relevant outcomes are 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 disease-associated variant in the family. In this situation, genetic testing will establish the presence or absence of the same variant in a close relative with a high degree of certainty. Presence of the variant indicates that the relative should undergo a cardiac evaluation upon receiving the variant-positive results. If a hypertrophic cardiomyopathy diagnosis is not made at that time, the patient should be monitored for development of symptoms. Absence of this variant 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. Such patients will 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 chain of evidence that management changes can improve outcomes with genetic testing when there is a known familial variant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with risk for HCM because of a positive family history who receive nonspecific testing for an HCM-related variant, the evidence includes studies reporting on the clinical validity of testing. Relevant outcomes are 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 variants have been identified, there is imperfect clinical sensitivity. Therefore, a negative test is not sufficient to rule out a disease-associated variant in patients without a known family variant. For at-risk individuals without a known variant in the family, there is no clear relation between testing and improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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FIRST DEGREE RELATIVE- refers to parent, sibling, or child.

SECOND DEGREE RELATIVE- refers to an aunt, uncle, niece, nephew, or grandparent.

THIRD DEGREE RELATIVE- refers to a great aunt/uncle, first cousin, or great grandmother/grandfather.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Not medically necessary; therefore, not covered:

Procedure Codes							
S3865	81439						

Covered when medically necessary:

Procedure Codes							
S3866	81403	81405	81406	81407	81479		

ICD-10-CM Diagnosis Codes:	Description
I42.1	Obstructive hypertrophic cardiomyopathy
I42.2	Other hypertrophic cardiomyopathy
Z13.71	Encounter for nonprocreative screening for genetic disease carrier status
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z82.41	Family history of sudden cardiac death
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system

IX. REFERENCES

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X. POLICY HISTORY

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MP-2.248	**CAC 6/26/12** New policy. Adopted BCBSA. Genetic testing for predisposition to inherited hypertrophic cardiomyopathy is considered medically necessary for specified criteria. FEP variation added.
	CAC 9/24/13 Consensus review. References updated but no changes to the policy statements. Rationale added.
	CAC 7/22/14 Consensus review. References and rationale updated but no changes to the policy statements
	CAC 7/21/15 Consensus review. No change to policy statements. References and rationale updated. No coding changes.
	CAC 7/26/16 Consensus review. Clarification made to the not medical necessary policy statement to indicate that familial testing should be in a family member with established HCM. Otherwise, policy statements unchanged. Background, references, and rationale updated. Policy Guidelines added. Appendix added. Coding reviewed.
	Administrative Update 11/23/16: Variation section reformatted.
	Administrative Update 1/1/17: Added new code 81439, effective 1/1/17.
	CAC 7/25/17 Consensus review. Policy statements unchanged. Medicare variation added. Description/Background, Rationale, and Reference sections updated. Coding Reviewed.
	1/1/18 Admin Update: Medicare variations removed from Commercial Policies
	4/3/18 Consensus review. No change to policy statements. Background and references updated. Rationale condensed to include only summary of evidence.
	2/20/19 Consensus review. No change to policy statements. References updated. **5/7/19** Coding review. No changes.
	3/2/20 Consensus review. No change to policy statement. Coding reviewed.

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	4/26/21 Consensus review. No change to policy statement. References added.
	4/27/22 Consensus review. No change to policy statement. Updated FEP, background, rationale, references. Coding reviewed.
	6/30/2023 Consensus review. Updated coding table; moved S3865 and 81439 to correct coding table (non-covered). Updated references.

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