Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
Current Effective Date: 04/13/2020

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 variant 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 variants 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.***

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
Current Effective Date: 04/13/2020

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 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 (eg, 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

The Human Genome Variation Society 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 Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the 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 for 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.

Background/Overview

Familial Hypertrophic Cardiomyopathy

Familial 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 (eg, Fabry disease, Pompe disease), and neuromuscular disorders (eg, 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 HCM and those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen) is a next-generation sequencing panel of 44 genes 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.

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 one 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.

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 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.

Rationale/Source

Familial hypertrophic cardiomyopathy (HCM) is an inherited condition caused by a disease-associated variant 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. Genetic testing for HCM-associated variants is available through a number of commercial laboratories.

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. The 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 an HCM 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. The 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.

Supplemental Information

Clinical Input 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.

In response to requests, input was received while this policy was under review in 2011. Input was solicited in January 2011 on general agreement with the policy and again 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 pathogenic variant. This vetting also asked whether testing should be restricted to first-degree relatives. To this question, there was a mixed response, with two reviewers indicating that they agreed 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 vetting focused on changes in management that could result from genetic testing. Reviewers were uniform that a positive test would result in heightened surveillance. All but one reviewer indicated that a negative test would 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 (2003).

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
Current Effective Date: 04/13/2020

Practice Guidelines and Position Statements

European Society of Cardiology
The European Society of Cardiology (2014) issued guidelines on the diagnosis and management of hypertrophic cardiomyopathy (HCM), which included the following recommendations related to genetic testing (see Table1).

Table 1. Guidelines on Diagnosis and Management of HCM

Recommendations	COR	LOE
Genetic counseling is recommended for all patients with HCM when their disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members	I	B
Genetic testing is recommended inpatients fulfilling diagnostic criteria for HCM when it enables cascade genetic screening of their relatives	I	B
It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations	I	C
In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis	I	B
Cascade genetic screening, after pre-test counseling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation	I	B
Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband	I	C
Genetic counseling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team	IIa	C
Genetic testing in patients with a borderline diagnosis of HCM should be performed only after detailed assessment by specialist teams	IIa	C
Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives	IIa	C

Recommendations	COR	LOE
First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family	IIa	B
When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2-5 years (or 6-12 monthly if non-diagnostic abnormalities are present)	IIa	C
The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing-following pre-test family counseling-when they are aged 10 or more years, and this should be carried out in accordance with international guidelines for genetic testing in children	IIa	C
In first-degree child relatives aged 10 or more years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1-2 years between 10 and 20 years of age, and then every 2-5 years thereafter	IIa	C
If requested by the parent(s) or legal representative(s), clinical assessment with ECG and echocardiography may precede or be substituted for genetic evaluation after counseling by experienced physicians and when it is agreed to be in the best interests of the child	IIb	C
When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical or genetic testing of first-degree child relatives before the age of 10 years may be considered	IIb	C
In definite mutation carriers who have no evidence of disease expression, sports activity may be allowed after taking into account the underlying mutation and the type of sports activity, and the results of regular and repeated cardiac examinations	IIb	C

COR: class of recommendation; ECG: electrocardiography; HCM: hypertrophic cardiomyopathy; LOE: level of evidence.

American College of Cardiology Foundation and American Heart Association
The ACC Foundation and the AHA (2011) issued joint guidelines on the diagnosis and treatment of HCM. Table 2 lists the recommendations on genetic testing.

Table 2. Joint Guidelines on Diagnosis and Treatment of HCM

Recommendations	COR	LOE
Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM	I	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	I	B
Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM	I	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	I	B
Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM	IIa	B
The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain	IIb	B
Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation	III	B
Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM	III	B

COR: class of recommendation; HCM: hypertrophic cardiomyopathy; LOE: level of evidence; SCD: sudden cardiac death.

I The ACC and AHA (2015) issued a joint scientific statement on the eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities. Fifteen Task Forces were assigned to review the scientific evidence for various cardiovascular diseases and with expert

consensus, develop recommendations for athletic participation. Table 3 outlines the recommendations related to HCM:

Table 3. ACC/AHA Recommendations for Participation in Sports

Recommendations	COR	LOE
Participation in competitive athletics for asymptomatic, genotype-positive HCM patients without evidence of LV hypertrophy by 2-dimensional echocardiography and CMR is reasonable, particularly in absence of a family history of HCM-related sudden death.	IIa	C
Athletes with a probable or unequivocal clinical expression and diagnosis of HCM (disease phenotype of LV hypertrophy) should not participate in most competitive sports, with the exception of class IA sports (low intensity).	III	C

CMR: cardiovascular magnetic resonance imaging; COR: class of recommendation; HCM: hypertrophic cardiomyopathy; LOE: level of evidence; LV: left ventricular; ACC: American College of Cardiology; AHA: American Heart Association.

Heart Rhythm Society and the European Heart Rhythm Association
The Heart Rhythm Society and the European Heart Rhythm Association (2011) published joint recommendations on genetic testing for cardiac channelopathies and cardiomyopathies.[41,] For HCM, the following recommendations (both class I) 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."

U.S. Preventive Services Task Force Recommendations
Not applicable

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01915615	HCMR - Novel Markers of Prognosis in Hypertrophic Cardiomyopathy	2750	Apr 2022
NCT00156429	Genetic Predictors of Outcome in HCM Patients	540	May 2020

NCT: national clinical trial.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy", Policy 2.02.28, 04:2019.
2. Semsarian C, Ingles J, Maron MS, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. Mar 31 2015;65(12):1249-1254. PMID 25814232
3. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. J Cardiovasc Electrophysiol. Jan 2008;19(1):104-110. PMID 17916152
4. Spirito P, Autore C, Formisano F, et al. Risk of sudden death and outcome in patients with hypertrophic cardiomyopathy with benign presentation and without risk factors. Am J Cardiol. May 1 2014;113(9):1550-1555. PMID 24630786
5. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. Nat Clin Pract Cardiovasc Med. Mar 2008;5(3):158-168. PMID 18227814
6. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol. Aug 21 2012;60(8):705-715. PMID 22796258
7. Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2014.

8. Ghosh N, Haddad H. Recent progress in the genetics of cardiomyopathy and its role in the clinical evaluation of patients with cardiomyopathy. Curr Opin Cardiol. Mar 2011;26(2):155-164. PMID 21297463
9. Teo LY, Moran RT, Tang WH. Evolving approaches to genetic evaluation of specific cardiomyopathies. Curr Heart Fail Rep. Dec 2015;12(6):339-349. PMID 26472190
10. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet. Jun 5 2004;363(9424):1881-1891. PMID 15183628
11. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. Nov 5 2003;42(9):1687-1713. PMID 14607462
12. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. Nov 8 2011;124(24):2761-2796. PMID 22068434
13. Arya A, Bode K, Piorkowski C, et al. Catheter ablation of electrical storm due to monomorphic ventricular tachycardia in patients with nonischemic cardiomyopathy: acute results and its effect on long-term survival. Pacing Clin Electrophysiol. Dec 2010;33(12):1504-1509. PMID 20636312
14. GeneDx. Personal Communication. April 29, 2010.
15. Correlagan. Personal Communication. April 27, 2010.
16. PGxHealth. Personal Communication. April 22, 2010.
17. ApolloGen. Comprehensive Cardiomyopathy Panel. https://www.ncbi.nlm.nih.gov/gtr/tests/525912/.
18. Das KJ, Ingles J, Bagnall RD, et al. Determining pathogenicity of genetic variants in hypertrophic cardiomyopathy: importance of periodic reassessment. Genet Med. Apr 2014;16(4):286-293. PMID 24113344
19. Andreasen C, Nielsen JB, Refsgaard L, et al. New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants. Eur J Hum Genet. Sep 2013;21(9):918- 928. PMID 23299917
20. Zou Y, Wang J, Liu X, et al. Multiple gene mutations, not the type of mutation, are the modifier of left ventricle hypertrophy in patients with hypertrophic cardiomyopathy. Mol Biol Rep. Jun 2013;40(6):3969-3976. PMID 23283745

21. BlueCross BlueShield Association Technology Evaluation Center (TEC). Genetic testing for predisposition to inherited hypertrophic cardiomyopathy. TEC Assessment. 2009;24(11).
22. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med. Apr 30 1998;338(18):1248-1257. PMID 9562578
23. Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. May 6 2003;107(17):2227-2232. PMID 12707239
24. Van Driest SL, Ommen SR, Tajik AJ, et al. Sarcomeric genotyping in hypertrophic cardiomyopathy. Mayo Clin Proc. Apr 2005;80(4):463-469. PMID 15819282
25. Van Driest SL, Jaeger MA, Ommen SR, et al. Comprehensive analysis of the beta-myosin heavy chain gene in 389 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. Aug 4 2004;44(3):602-610. PMID 15358028
26. Van Driest SL, Ellsworth EG, Ommen SR, et al. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. Circulation. Jul 29 2003;108(4):445-451. PMID 12860912
27. Mogensen J, Murphy RT, Kubo T, et al. Frequency and clinical expression of cardiac troponin I mutations in 748 consecutive families with hypertrophic cardiomyopathy. J Am Coll Cardiol. Dec 21 2004;44(12):2315-2325. PMID 15607392
28. Michels M, Soliman OI, Phefferkorn J, et al. Disease penetrance and risk stratification for sudden cardiac death in asymptomatic hypertrophic cardiomyopathy mutation carriers. Eur Heart J. Nov 2009;30(21):2593-2598. PMID 19666645
29. Cardoso B, Gomes I, Loureiro P, et al. Clinical and genetic diagnosis of familial hypertrophic cardiomyopathy: Results in pediatric cardiology. Rev Port Cardiol. Mar 2017;36(3):155-165. PMID 28214152
30. van Velzen, HH, Schinkel, AA, Baart, SS, Oldenburg, RR, Frohn-Mulder, II, van Slegtenhorst, MM, Michels, MM. Outcomes of Contemporary Family Screening in Hypertrophic Cardiomyopathy. Circ Genom Precis Med, 2018 Apr 18;11(4). PMID 29661763
31. Ko, CC, Arscott, PP, Concannon, MM, Saberi, SS, Day, SS, Yashar, BB, Helms, AA. Genetic testing impacts the utility of prospective familial screening in hypertrophic cardiomyopathy through identification of a nonfamilial subgroup. Genet. Med., 2017 Jun 24;20(1). PMID 28640247
32. Lopes, LL, Brito, DD, Belo, AA, Cardim, NN. Genetic characterization and genotype-phenotype associations in a large cohort of patients with hypertrophic cardiomyopathy - An ancillary study

of the Portuguese registry of hypertrophic cardiomyopathy. Int. J. Cardiol., 2018 Dec 18;278:173-179. PMID 30554928
33. Sedaghat-Hamedani, FF, Kayvanpour, EE, Tugrul, OO, Lai, AA, Amr, AA, Haas, JJ, Proctor, TT, Ehlermann, PP, Jensen, KK, Katus, HH, Meder, BB. Clinical outcomes associated with sarcomere mutations in hypertrophic cardiomyopathy: a meta-analysis on 7675 individuals. Clin Res Cardiol, 2017 Aug 26;107(1). PMID 28840316
34. Erdmann J, Daehmlow S, Wischke S, et al. Mutation spectrum in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy. Clin Genet. Oct 2003;64(4):339-349. PMID 12974739
35. Olivotto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc. Jun 2008;83(6):630-638. PMID 18533079
36. Chiou KR, Chu CT, Charng MJ. Detection of mutations in symptomatic patients with hypertrophic cardiomyopathy in Taiwan. J Cardiol. Mar 2015;65(3):250-256. PMID 25086479
37. Adalsteinsdottir B, Teekakirikul P, Maron BJ, et al. Nationwide Study on Hypertrophic Cardiomyopathy in Iceland: Evidence of a MYBPC3 Founder Mutation. Circulation. Sep 30 2014;130(14):1158-1167. PMID 25078086
38. Ingles, JJ, Goldstein, JJ, Thaxton, CC, Caleshu, CC, Corty, EE, Crowley, SS, Dougherty, KK, Harrison, SS, McGlaughon, JJ, Milko, LL, Morales, AA, Seifert, BB, Strande, NN, Thomson, KK, van Tintelen, JJ, Wallace, KK, Walsh, RR, Wells, QQ, Whiffin, NN, Witkowski, LL, Semsarian, CC, Ware, JJ, Hershberger, RR, Funke, BB. Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes. Circ Genom Precis Med, 2019 Jan 27. PMID 30681346
39. Authors/Task Force m, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. Oct 14 2014;35(39):2733-2779. PMID 25173338
40. Maron, BB, Zipes, DD, Kovacs, RR. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Preamble, Principles, and General Considerations: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation, 2015 Dec 2;132(22). PMID 26621642
41. Maron, BB, Udelson, JJ, Bonow, RR, Nishimura, RR, Ackerman, MM, Estes, NN, Cooper, LL, Link, MM, Maron, MM. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and

Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. J. Am. Coll. Cardiol., 2015 Nov 7;66(21). PMID 26542657

42. 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: 04/13/2020

08/16/2001	Medical Policy Committee review
08/27/2001	Managed Care Advisory Council approval
03/21/2002	Medical Policy Committee review. Coverage eligibility changed to reflect current literature.
03/25/2002	Managed Care Advisory Council approval
02/03/2004	Medical Director Review
02/17/2004	Medical Policy Committee review. Format revision. Coverage eligibility change to reflect the investigational status of the technology identified in current literature.
02/23/2004	Managed Care Advisory Council approval. Claims Processing effective date based on revised policy will be 4/1/04.
02/01/2006	Medical Director review
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.

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
Current Effective Date: 04/13/2020

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.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270
Original Effective Date: 04/25/2012
Current Effective Date: 04/13/2020

Next Scheduled Review Date: 3/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	81403, 81405, 81406, 81407, 81439, 81479
HCPCS	G0452, S3865, S3866
ICD-10 Diagnosis	I42.0-I42.9, Z13.71, Z13.79, Z13.89, Z82.41, Z82.49

*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. Food and Drug Administration (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 technology assessment program (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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.