



Louisiana

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

Policy # 00270

Original Effective Date: 04/25/2012

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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**.*

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 also 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 a number of different protein structures. Around 1400 disease-associated variants in at least 18 different genes have been identified. Approximately 90% of pathogenic variants are missense (ie, 1 amino acid is replaced for another), and the strongest evidence for pathogenicity is

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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 clinically documented disease are demonstrated to have a familial pattern, although some exceptions are found presumably due to de novo variants.

Diagnosis

The clinical diagnosis of HCM depends on the presence of left ventricular hypertrophy (LVH), measured by echocardiography or magnetic resonance imaging, in the absence of other known causative factors such as valvular disease, long-standing hypertension, or other myocardial disease. 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 (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 of all HCM patients, 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. ICD 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 in 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.

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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 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.

Commercial testing has been available since May 2003, and numerous companies currently offer genetic testing for HCM. Testing is performed either as comprehensive testing or targeted gene testing. Comprehensive testing, which is done for an individual without a known genetic variant in the family, analyzes the genes that are 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*), X-linked Danon disease (*LAMP2*).

Other panels include testing for genes related to HCM but also those associated with other cardiac disorders. For example, the Comprehensive Cardiomyopathy panel (ApolloGen, Irvine, CA) is a next-generation sequencing (NGS) 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 NGS 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 NGS. In addition, 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.

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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Sequencing tests for HCM are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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There are no assay kits approved by FDA for genetic testing for HCM.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). Following is a summary of the key literature.

The TEC Assessment reviewed the evidence on the accuracy of genetic testing in identifying patients who will subsequently develop HCM and identified 7 studies meeting inclusion criteria.

TESTING FOR A SPECIFIC HCM-RELATED VARIANT

Clinical Context and Test Purpose

The purpose of targeted genetic testing in patients who are asymptomatic but at risk of HCM is to inform management decisions. Genetic testing for HCM may potentially play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

The question addressed in this evidence review is whether testing an asymptomatic individual for a family variant known to be associated with HCM improves outcomes by obviating the need for routine surveillance if the result is negative.

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is asymptomatic individuals with a close relative who has HCM and a known pathogenic variant.

Interventions

Targeted genetic testing on the variant(s) identified in the relative with HCM.

Comparators

The comparator of interest is standard clinical management without genetic testing such that decisions related to surveillance and medical therapy are based on guidelines for patients with a relative with HCM.

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Outcomes

If the test has a high negative predictive value, the main beneficial outcome would be to safely reduce or eliminate the need for routine clinical surveillance for signs and symptoms of HCM.

Potential harmful outcomes are those resulting from a false test result. False-positive results can lead to initiation of unnecessary treatment and adverse effects from that treatment. False-negative results could lead to delay in diagnosis and treatment.

Timing

Appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of onset of HCM from genetic causes. Changes in outcomes due to increased surveillance or early initiation of treatment in asymptomatic patients would take many years to become evident.

Setting

Family members of individuals diagnosed with HCM may be referred to a secondary or tertiary care setting for clinical screening and genetic testing. Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity

For predispositional genetic testing, the analytic validity (ability to detect or exclude a *specific* variant; in this case, the specific variant of interest is a variant identified in another family member) were evaluated. The analytic validity is more relevant when there is a known variant in the family, whereas the clinical validity is more relevant for individuals without a known variant in the family.

The analytic sensitivity (probability that a test will detect a specific variant that is present) of sequence analysis for detecting variants that cause HCM is likely to be very high based on what is known about the types of variants that cause HCM and the limited empirical data provided by manufacturers and detailed descriptions of the testing methodology. There are fewer data available on the analytic specificity (probability that a test will be negative when a specific variant is absent) 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 variants are uncommon.

Therefore, for a patient with a known variant in the family, the high analytic validity means that targeted genetic testing for a familial variant has high predictive value for both a positive (variant detected) and a negative (variant not detected) test result. A negative test indicates that the individual is free of the variant, while a positive test indicates that the patient has the variant and is at risk for developing HCM in the future.

Clinical Validity

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

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pathogenic variant will eventually develop the condition of concern. There is reduced penetrance in HCM (ie, not everyone with a deleterious variant will develop manifestations of HCM). In addition, penetrance varies among different variants and may even vary among different families with an identical pathogenic variant. As a result, it is not possible to estimate accurately the penetrance for any given variant in a specific family.

Multiple pathogenic variants are found in 1% to 10% of patients with HCM and are associated with more severe disease and a worse prognosis. For these patients, targeted analysis may miss variants other than the one tested for. Some experts recommend comprehensive testing of all individuals for this reason; however, it is not known whether the presence of multiple pathogenic variants influences management decisions such that health outcomes might be improved.

Clinical Utility

Predictive Testing: Detection in At-Risk Individuals

There are benefits to predisposition genetic testing for at-risk individuals when there is a known disease-associated variant in the family. Inheritance of the predisposition to HCM can be ruled out with near certainty when the genetic test is negative (variant not detected) in this circumstance. A positive test result (variant detected) is less useful. It confirms the presence of a pathogenic variant 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.

Michels et al (2009) attempted to risk-stratify asymptomatic patients with a positive genetic test for HCM. They reported cardiac evaluation outcomes and risk stratification for SCD in 76 asymptomatic HCM variant carriers identified from 32 families. Between 2007 and 2008, 76 asymptomatic family members of 32 probands with HCM and known variants were found to have variants in 1 or more genes. HCM was diagnosed in 31 (41%) asymptomatic family members. The authors attempted to risk-stratify patients for SCD, and found that none of the screened carriers was symptomatic, had a history of syncope, or had severe hypertrophy (≥ 30 mm). Four carriers were found to have an abnormal blood pressure response during exercise, which is associated with worse prognosis; of those, 3 were diagnosed with HCM. Three carriers were found to have nonsustained ventricular tachycardia, which is also associated with worse prognosis in HCM; of those, 2 were diagnosed with HCM. The study did not have sufficient follow-up to determine whether these risk factors were associated with differences in SCD rates over the long term.

At present, the management of patients with HCM is not dependent on the identification of a specific variant or any positive variant testing results. However, there is active investigation into treatments that may slow disease progression before the development of overt echocardiographic signs of HCM.

Carrier Testing: Variant Detection for Reproductive Decision Making

Knowledge of the results of genetic testing may aid in decision making on such issues as reproduction by informing discussion on the susceptibility to develop future disease. Direct evidence on the impact of

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genetic information on this type of decision making is lacking, and the effect of such decisions on health outcomes is uncertain.

Additionally, rudimentary disease prevention based on assisted reproduction using preimplantation genetic diagnosis (PGD) is possible. PGD uses in vitro fertilization with a single cell removed from early-stage embryos and tested for the familial variant. Only those embryos without the identified HCM variant are used to initiate pregnancy. Disease-modifying studies are in development using animal models of HCM. In rodent models, sarcomere variants have been implicated in early abnormal intracellular calcium handling far in advance of LVH. Treatment of this calcium handling by use of diltiazem appeared to attenuate the development of LVH when started in early life. Kristyn feasibility of this strategy in humans has been assessed in a pilot randomized controlled trial that compared diltiazem to placebo in known sarcomere variant carriers who have yet to develop LVH.

Section Summary: Testing for a Specific HCM-Related Variant

The available evidence on testing for variants related to HCM indicates a high analytic sensitivity and specificity. This suggests that, in cases where there is interest in identifying a specific variant (ie, when there is a known variant in an affected family member), testing can rule in or rule out the presence of a variant with high certainty. On the other hand, variability in clinical penetrance means that a positive genetic test does not rule in clinical HCM, although it makes HCM more likely. The available evidence has not demonstrated that specific genetic testing results are associated with a HCM-related phenotype or disease penetrance. Use of genetic testing for HCM has the greatest utility in asymptomatic family members of patients with HCM who have a known genetic variant. Given the high sensitivity for *known* variants, the absence of a variant in the asymptomatic relatives should rule out the presence of familial HCM and allow reduction in surveillance for complications. Detection of variants in asymptomatic carriers may aid reproductive decision making, although direct evidence is limited on the impact of genetic information in this setting.

NONSPECIFIC TESTING FOR A HCM-RELATED VARIANT

Clinical Context and Test Purpose

The purpose of nonspecific genetic testing in patients who are asymptomatic but at risk of HCM is to inform management decisions. Genetic testing for HCM could play a role in several clinical situations. Situations considered here are genetic testing for disease prediction in at-risk individuals and genetic testing for reproductive decision making.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic individuals at risk of developing HCM?

The following PICOTS were used to select literature to inform this review.

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Patients

The relevant population of interest is individuals who are asymptomatic with a close relative who has HCM and an unknown pathogenic variant.

Interventions

Nontargeted genetic testing.

Comparators

The comparator of interest is standard clinical management without genetic testing such that decisions on surveillance and medical therapy are based on guidelines for patients with a relative with HCM.

Outcomes

The general outcomes of interest are overall survival, test accuracy and validity, changes in reproductive decision making, symptoms, and morbid events.

The potential beneficial outcome of primary interest would be reduction in surveillance for the development of HCM. Maintenance of functioning and quality of life are also important.

Potential harmful outcomes are those resulting from a false result. False-positive test results can lead to initiation of unnecessary treatment and adverse effects from that treatment. False-negative test results could lead to delay in diagnosis and treatment.

Timing

Appropriate length of follow-up is complicated by the varying ages of close relatives (parents, siblings, children) and variation in age of HCM onset from genetic causes. Changes in outcomes due to increased surveillance or early initiation of treatment in asymptomatic patients would take many years to become evident.

Setting

Family members of individuals diagnosed with HCM may be referred to a secondary or tertiary care setting for clinical screening and genetic testing. Genetic counseling is important for providing family members with an explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity

There is some published evidence on the analytic validity of next-generation sequencing panels for genes associated with cardiomyopathies, including HCM. For example, one 17-gene panel was reported to have a maximum 96.7% sensitivity for single-nucleotide variants, with positive predictive values above 95%, compared with Sanger sequencing. The rate of false-positive results is likely to be higher for classification of previously unknown variants.

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Clinical Validity

Clinical validity for nonspecific testing is the ability to detect *any* pathogenic variant in a patient with HCM and to exclude a variant in a patient without HCM. The clinical validity of genetic testing for HCM is considerably lower than the analytic validity. Evidence on clinical sensitivity (probability that a person with HCM, or who will get HCM, will have a positive genetic test result), consists of several case series of patients with established HCM. To date, the published variant detection rate ranges from 33% to 67%. The less-than-perfect variant 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 variant scanning methods such as single-strand conformation polymorphism or denaturing gradient gel electrophoresis that will miss certain deleterious variants. Another reason for the less-than-perfect variant detection rate is that other, as yet unidentified, genes may be responsible for HCM. Finally, there may be unknown, nongenetic factors that mimic HCM. Variant detection rates will likely increase over time with recognition of new variants.

Clinical Utility

If a familial variant is not known and an at-risk individual undergoes testing, a positive result (variant detected) would confirm an inherited predisposition to HCM and an increased risk for clinical manifestations in the future. However, a negative result (no variant detected) could not exclude the possibility that a variant 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 variant is not known, comprehensive variant 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.

Section Summary: Nonspecific Testing for a HCM-Related Variant

Given the wide genetic variation in HCM and the likelihood that not all causative variants have been identified, there is imperfect clinical sensitivity. Because of the imperfect clinical sensitivity, a negative test is not sufficient to rule out HCM in patients without a known variant in the family.

Because of the suboptimal clinical sensitivity relating to less-than-perfect variant detection, the best genetic testing strategy for predisposition testing for HCM begins with comprehensive testing (eg, sequence analysis) of a DNA sample from an affected family member. Comprehensive variant analysis in an index patient is important because it informs and directs the subsequent testing of at-risk relatives. If the same variant 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 variant is not identified in an at-risk relative, then this confirms that the variant has not been inherited, and there is then 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 the patient can be reassured that his or her risk of developing the disease is no greater than that of the general population.

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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 analytic and 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. 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 a HCM-related variant, the evidence includes studies reporting on the analytic and 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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy", Policy 2.02.28, 03:2017.
2. Ramaraj R. Hypertrophic cardiomyopathy: etiology, diagnosis, and treatment. *Cardiol Rev.* Jul-Aug 2008;16(4):172-180. PMID 18562807
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. Marian AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol.* May 2008;23(3):199-205. PMID 18382207
5. Roberts R, Sigwart U. Current concepts of the pathogenesis and treatment of hypertrophic cardiomyopathy. *Circulation.* Jul 12 2005;112(2):293-296. PMID 16009810
6. 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
7. 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
8. Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. *GeneReviews.* 2008 (updated 2014). PMID 20301725
9. 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

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10. 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
11. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet*. Jun 5 2004;363(9424):1881-1891. PMID 15183628
12. 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
13. 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
14. 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
15. GeneDx®. Personal Communication. April 29, 2010.
16. Correlagan®. Personal Communication. April 27, 2010.
17. PGxHealth®. Personal Communication. April 22, 2010.
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. Andreassen 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. Harvard CardioGenomics website. 2010; <http://cardiogenomics.med.harvard.edu/home>.
23. 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
24. 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
25. Olivetto I, Girolami F, Ackerman MJ, et al. Myofibrillar protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc*. Jun 2008;83(6):630-638. PMID 18533079
26. 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
27. 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
28. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med*. Apr 20 1995;332(16):1058-1064. PMID 7898523
29. Charron P, Carrier L, Dubourg O, et al. Penetrance of familial hypertrophic cardiomyopathy. *Genet Couns*. 1997;8(2):107-114. PMID 9219008
30. Fananapazir L, Epstein ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy. Insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. *Circulation*. Jan 1994;89(1):22-32. PMID 8281650
31. Michels M, Soliman OI, Pfefferkorn 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
32. Axelsson A, Iversen K, Vejstrup N, et al. Efficacy and safety of the angiotensin II receptor blocker losartan for hypertrophic cardiomyopathy: the INHERIT randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. Feb 2015;3(2):123-131. PMID 25533774
33. Ho CY, Lakdawala NK, Cirino AL, et al. Diltiazem treatment for pre-clinical hypertrophic cardiomyopathy sarcomere mutation carriers: a pilot randomized trial to modify disease expression. *JACC Heart Fail*. Feb 2015;3(2):180-188. PMID 25543971
34. Oliveira TG, Mitne-Neto M, Cerdeira LT, et al. A variant detection pipeline for inherited cardiomyopathy-associated genes using next-generation sequencing. *J Mol Diagn*. Jul 2015;17(4):420-430. PMID 25937619

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35. Chiou KR, Chu CT, Chang MJ. Detection of mutations in symptomatic patients with hypertrophic cardiomyopathy in Taiwan. *J Cardiol.* Mar 2015;65(3):250-256. PMID 25086479
36. 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
37. 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
38. 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

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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.
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.

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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.
 Next Scheduled Review Date: 3/2019

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 2017 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.

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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. 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:

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1. Consultation with the Blue Cross and Blue Shield Association 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.

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