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Medical Coverage Policy

Effective Date 3/15/2024
Next Review Date 3/15/2025
Coverage Policy Number.....0517

Genetic Testing for Hereditary Cardiomyopathies and Arrhythmias

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must

use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses several types of testing for harmful or likely harmful changes in the genetic information of eggs and sperm, also known as germ cells, related to certain cardiomyopathies and cardiac arrhythmias. The changes are known as germline gene variants. Germline gene variants are inherited; that is, passed down in families by blood relatives.

A cardiomyopathy is a disorder that affects the heart muscle, causing it to lose its ability to pump blood well. Types of inherited cardiomyopathies are hypertrophic, where the heart muscle becomes thickened, dilated, where the heart is enlarged, arrhythmogenic , where the heart muscle is replaced by scar tissue), non-compaction, where the heart muscle doesn't fully form and restrictive, where the heart doesn't fill with blood or contract properly.

Inherited cardiac arrhythmias are caused by gene changes that affect the function of the heart's electrical system, although the heart muscle itself may be normal. These changes can cause abnormal heart beats which may cause life-threatening conditions such as sudden cardiac death, where the heart stops beating and ventricular tachycardia, where the heart beats too fast.

Testing discussed in this Coverage Policy include testing for changes in a single gene and testing for multiple changes in a gene or genes. Also discussed are tests that measure how the action of a gene is turned on or off, which is referred to as gene expression. Test results can help determine the risk for or presence of a condition and can help decide on a treatment.

Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

Pre- and post-test genetic counseling is required for any individual undergoing genetic testing for the hereditary cardiomyopathies and arrhythmias discussed in this Coverage Policy. Please refer to disease specific criteria* for additional information regarding genetic testing.

GENERAL GENETIC TESTING CRITERIA-REQUIREMENT FOR GENETIC COUNSELING

Genetic testing is considered medically necessary when disease specific criteria* for the hereditary cardiomyopathies and/or arrhythmias listed below are met and when a recommendation for testing is confirmed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist

- an American Board of Medical Genetics or American Board of genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Clinical Genomics Nurse (CGN) or an Advanced Clinical Genomics Nurse (ACGN) by the Nurse Portfolio Credentialing Commission, Inc. or a genetic nurse with an Advanced Genetics Nursing Certification (AGN-BC) renewed by the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

  who:

  - has evaluated the individual
  - completed a three-generation pedigree
  - intends to engage in post-test follow-up counseling

CONFIRMATORY (DIAGNOSTIC) GENETIC TESTING

Confirmatory (i.e., diagnostic) single gene or multi-gene testing for a hereditary cardiomyopathy and/or arrhythmia is considered medically necessary when ALL of the following criteria are met:

- The individual has a confirmed clinical diagnosis of: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), Long QT syndrome (LQTS), Brugada syndrome (BrS), or catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Acquired etiologies have been excluded
- Testing is targeted to a specific subset of genes related to the suspected condition
- ANY of the following criteria are met:
  - results with directly impact clinical decision making and/or clinical outcomes for the individual being tested
  - individual has an at-risk first- or second-degree blood relative
  - the individual or the individual's reproductive partner, parent, or biological offspring has the capacity and intention to reproduce and genetic test results will be used for reproductive decision-making

PREDICTIVE GENETIC TESTING

Predictive testing is considered medically necessary for ANY of the following:

- prolonged QT interval on ECG or Holter monitor (i.e., corrected QT [QTc] interval of >470 msec [males] or >480 msec [females]) in a first-degree relative*, the affected individual is not available for testing, and testing is targeted to LQTS
- near sudden unexplained death at age 40 or younger when acquired etiologies have been ruled out and there is no evidence of ischemia
- single site genetic testing for ARVC/D, HCM, DCM, RCM, BrS, LQTS, or CPVT when there is a known familial pathogenic or likely pathogenic variant in a first- or second-degree relative*

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

OTHER GENETIC TESTING SERVICES

Genetic testing for atrial fibrillation, short QT syndrome and left ventricular noncompaction cardiomyopathy (LVNC) is considered not medically necessary.

Genetic testing for broad, multi-condition, panel testing is considered not medically necessary when a specific cardiac phenotype has been identified.

Polygenic risk score testing is considered not medically necessary.

Genetic testing for hereditary cardiac conditions in the general population is considered not medically necessary.

General Background

Genetic Counseling

Genetic counseling is required both pre-and post- genetic testing for the hereditary cardiomyopathies and arrhythmias discussed in this Coverage Policy to interpret family and medical histories and assess the chance of disease occurrence and recurrence. Genetic counseling also allows an opportunity to educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition.

Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis (National Society of Genetic Counselors [NSGC]; Edwards, 2010).

A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and a genetic nurse credentialed as a Clinical Genomics Nurse (CGN) or an Advanced Clinical Genomics Nurse (ACGN) by the Nurse Portfolio Credentialing Commission, Inc. or a genetic nurse with an Advanced Genetics Nursing Certification (AGN-BC) renewed by the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

Genetic Testing

Genetic testing has been proposed as a method to differentiate inherited or familial cardiomyopathies and arrhythmias from those caused by other factors. Cardiomyopathies are a heterogeneous group of acquired or inherited disorders affecting the heart muscle's ability to contract and to relax. They are described by their effect on the heart muscle and include hypertrophic (HCM) (e.g., thickened), dilated (DCM) (e.g., stretched out) and restrictive (RCM) (e.g., stiffened).

Like the cardiomyopathies discussed above, Long QT (LQTS), Brugada (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndromes (SQTS) are characterized by symptoms which can develop rapidly and can be life-threatening, including an increased risk of sudden cardiac death, also known as sudden cardiac arrest.

Incomplete penetrance within families and variable expressivity of symptoms is characteristic of inherited cardiomyopathies and arrhythmias and makes the clinical usefulness of genetic testing challenging. Individuals may have few symptoms and require no treatment. Depending on the gene involved, inheritance patterns differ within defined syndromes and arrhythmias. These include an autosomal dominant pattern (e.g., DCM, HCM, RCM, ARVD/C, LQTS, BrS, SQTS) and an autosomal recessive pattern (e.g., DCM, LQTS). Other cardiomyopathies result from a new gene variant (i.e., de novo) with no history of cardiomyopathy in the family (e.g., RCM, DCM) while for others, an X-linked pattern of inheritance is present (e.g., DCM).

Some inherited cardiac disorders present as a phenotype, such as the cardiomyopathies.

Confirmatory (Diagnostic) Genetic Testing
Many hereditary cardiomyopathies and arrhythmias are diagnosed clinically using results of EKGs, MRIs and cardiac echocardiogram. When an individual has a suspected, but not confirmed, clinical diagnosis of a specific hereditary cardiomyopathy or arrhythmia, confirmatory (i.e., diagnostic) genetic testing may be appropriate. Testing should be targeted to a specific subset of genes related to the individual's suspected condition and results of testing should directly impact clinical decision-making and/or the clinical outcome of the individual being tested.

Diagnostic testing may also be appropriate to determine if there is a pathogenic variant in an individual who has been diagnosed with HCM, CPVT, DCM, Brugada syndrome, ARVC/D or RCM. Clarification of the genetic status of at-risk family members allows longitudinal evaluation to be focused on those who have inherited the pathogenic variant of the condition in question (GeneReviews, 2017, 2016, 2015, 2014). In contrast to HCM, DCM, RCM and ARVC, the left ventricular non-compaction (LVNC) phenotype remains without consensus as to whether it is a primary cardiomyopathy, a variant morphologic trait or something else. Guidelines from the Heart Failure Society refer to it as a phenotype. According to imaging evidence, non-compaction of the myocardium is present in 2-10% of the population. Further, it may progress and regress. Testing for gene variants related to this phenotype would be included in testing for the primary cardiomyopathy (Hershberger et al., 2018). Therefore, genetic testing for LVNC is not separately recommended.

Requests for prenatal testing for hereditary cardiomyopathies or arrhythmias are not common. However, diagnostic molecular testing may be appropriate for reproductive decision-making when an individual has a clinical diagnosis of hypertrophic cardiomyopathy (HCM), CPVT, DCM, Brugada syndrome, ARVC/D or RCM. Testing should be targeted to the disorder(s) corresponding to the individual's clinical diagnosis, and the individual, the individual's reproductive partner or parent should have the capacity and intention to reproduce.

Predictive Genetic Testing
Predictive testing targeted to LQTS of an at-risk blood relative by full sequence analysis is appropriate when there is a history of prolonged QT interval on ECG or Holter monitor in an affected first-degree blood relative, but the relative is not available for testing. Deletion/duplication analysis may be appropriate if sequence analysis fails to detect variants. Other circumstances where predictive testing has clinical usefulness include the sudden death with a suspected cardiac diagnosis in a first degree blood relative or near sudden death at age 40 or younger with no evidence of ischemia. When the familial variant is known, predictive genetic testing for the known familial sequence variant evidence is appropriate.

Several studies have been published in the peer-reviewed scientific literature that indicate genetic testing for LQTS may offer early identification of those patients at high risk to develop LQTS and may provide the opportunity for early intervention (Imboden, et al., 2006; Behr, et al., 2003; Priori, et al., 2003). Genetic testing for LQTS has clinical usefulness in long-term management including lifestyle modification and the potential for use of beta-adrenergic blockers, permanent pacemaker implantation and implantable cardioverter defibrillators placement.

Single site testing may be appropriate in an at-risk individual if a familial variant has been identified in a first- or second-degree relative for a number of inherited cardiomyopathies (i.e., HCM, RCM, ARVD/C) and inherited arrhythmias (BrS, CVPT). The clinical utility of such genetic testing, especially in children or adolescents, is the ability to determine whether or not close monitoring or continued surveillance in the form of lab testing, electrocardiograms, echocardiograms, stress testing, cardiac MRI and other diagnostic interventions or activity restriction is required. If there is a known familial variant, a negative test in an at-risk family member can rule out predisposition to the disorder in question and there is no need for continued surveillance. Although a positive result does not ensure that an individual will develop the disorder, this information may assist in establishing a plan for monitoring.

Professional Society/Organizations
European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) (2022): Wilde et al., published an expert consensus statement on the state of genetic testing for cardiac diseases. The consensus document notes:

- Genetic testing in patients with a potential cardiogenetic condition is performed only with appropriate genetic counselling.
- In patients with a clear specific phenotype, it is appropriate to perform genetic testing analysing genes with definite or strong evidence supporting disease causation.
- In patients with a clear specific phenotype, it may be appropriate to analyse genes with moderate evidence supporting disease causation.
- In selected cases with a definite phenotype and no genetic diagnosis after testing of the genes with definite or strong evidence supporting disease causation, broader genetic testing may be considered. Such selected cases may include familial cases, those with atypical features, such as extracardiac manifestations and those with unusual early disease onset.
- Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multidisciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists.
- Variant interpretation is best performed using standard guidelines for interpretation and can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration.
- Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting.
- In patients with a high probability of a specific inherited cardiac disease and a molecular screening performed in a pre-NGS era or with an incomplete NGS panel, repetition of the testing should be considered.

American College of Cardiology/American Heart Association Joint Committee on Clinical Practice: On behalf of the ACC/AHA, Ommen et al. (2020) published Guidelines regarding the diagnosis and treatment of hypertrophic cardiomyopathy. The Guidelines included the following recommendations for genetic testing:

- Counseling patients with HCM regarding the potential for genetic transmission of HCM is one of the cornerstones of care.
- Screening first-degree family members of patients with HCM, using either genetic testing or an imaging/electrocardiographic surveillance protocol, can begin at any age and can be influenced by specifics of the patient/family history and family preference. As screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years.

American Heart Association (AHA, 2020): On behalf of the AHA Musunuru et al., published a Scientific Statement regarding genetic testing for inherited cardiac diseases.
The statement notes the role of genetic testing for the following conditions:

- Brugada syndrome:
  - can support clinical diagnosis
  - aids with identification of family members at risk for the condition
- Catecholaminergic polymorphic ventricular tachycardia:
  - major criterion for diagnosis and subtype classification
  - aids with identification of family members at risk for the condition
- Long-QT syndrome:
  - confirm clinical diagnosis and subtype classification
  - identification of causative gene may affect recommended treatment/therapeutic decisions and risk assessment
  - aids with identification of family members at risk for the condition
- ARVC:
  - major criterion for diagnosis and subtype classification
  - aids with identification of family members at risk for the condition
- HCM/DCM:
  - can support clinical diagnosis and subtype classification
  - aids with identification of family members at risk for the condition
- Restrictive cardiomyopathy:
  - confirm clinical diagnosis
  - identification of causative gene can guide choice of therapy
  - aids with identification of family members at risk for the condition

Heart Failure Society of America ([HFSA], 2018): On behalf of the HFSA Lindenfield et al. published guidelines for the genetic evaluation of cardiomyopathy. The guidelines note:

- Because results may guide management, we recommend genetic testing at the time a new cardiomyopathy diagnosis is made, but it can be conducted at any time after diagnosis.
- Education and counseling regarding genetic testing options are a key component of the process.
- For those who have had genetic testing in the past, retesting may be appropriate if the previous testing produced negative or inconclusive results and the test's detection rate has improved. This latter point is particularly relevant for DCM, because the gene panels have rapidly expanded (eg, inclusion of TTN15,82,83 and others) and are expected to continue expanding.
- Molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardiovascular genetic medicine. Furthermore, multigene panel genetic testing is recommended over a serial single-gene testing approach owing to the genetically heterogeneous nature of cardiomyopathy

Other Genetic Testing Services

Inherited Atrial Fibrillation: Inherited or familial atrial fibrillation is characterized by

uncoordinated electrical activity in the atria. Symptoms of familial atrial fibrillation are indistinguishable from atrial fibrillation from non-genetic causes and include dizziness, chest pain, a sensation of fluttering or pounding in the chest (palpitations), shortness of breath, syncope and an increased risk of stroke and sudden death. Some individuals with inherited atrial fibrillation do not experience these symptoms.

The incidence of the familial form of atrial fibrillation is unknown. The majority of atrial fibrillation can be attributed to underlying structural heart disease (Judge, 2012). Variations in three genes have been identified (i.e., KCNE2, KCNJ2, KCNQ1) and genetic testing for these variants is clinically available (National Institutes of Health, 2017); however, the majority of cases of atrial fibrillation are not caused by a gene variant. Standard treatment includes history and physical, electrocardiography and rhythm monitoring. Although genetic risk scores are highly associated with atrial fibrillation, genetic information currently affords small improvements in discrimination of risk (Lubitz, 2017). Such testing is not yet considered the standard of care for the treatment or management of atrial fibrillation (January, et al., 2014). The role of genetic testing for this indication is not supported by published consensus guidelines.

Professional Society/Organizations
Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) (2011): On behalf of the HRS/EHRA Ackerman et al. (2011) published an expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. The statement notes:

- Genetic testing is not indicated for atrial fibrillation at this time. (Class III, "Should not" or "is not recommended.")
- Single nucleotide polymorphism (SNP) genotyping in general and SNP rs2200733 genotyping at the 4q25 locus for AF is not indicated at this time based on the limited outcome data currently available. (Class III, Class III, "Should not" or "is not recommended.")

American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society (2014): On behalf of these societies, January et al. published guidelines related to the management of atrial fibrillation. The role of common genetic variants in risk stratification, assessment of disease progression, and determination of clinical outcomes is limited. According to the guideline the routine genetic testing related to AF is not indicated.

Short QT syndrome (SQTS): SQTS is a rare genetically heterogeneous condition associated with a predisposition to ventricular and atrial fibrillation and sudden cardiac death. Approximately 100 cases have been identified since the condition was recognized in 2001. The heart is structurally normal, but the time to recharge between beats is shortened which is exhibited on the electrocardiograph as an abbreviated or shortened QT interval (National Institutes of Health, 2015). The phenotype varies and may be characterized by no clinical symptoms to dizziness and fainting, or may include cardiac arrest and sudden cardiac death. Six types of SQTS (1-6) have been identified; however, data is limited in the published peer-reviewed scientific literature regarding genotype-phenotype correlation. Data is also lacking regarding treatment options targeted to genotype.

Genetic testing has been proposed to determine if a genetic variant is present in an individual with SQTS. Six genes (three gain of function and three loss of function) have been identified. SQTS is transmitted in an autosomal dominant fashion, although rarely sporadic inheritance has been identified. Several genes identified in SQTS are the same as those responsible for LQTS; however, the variations in SQTS increase repolarizing forces which is an effect opposite to that which occurs in LQTS.

There is insufficient evidence in the published peer-reviewed scientific literature regarding the clinical utility of genetic testing for SQTS to establish a genotype-phenotype correlation, stratify risk for developing SQTS or assign treatment if a variant is present. Treatment for sudden cardiac death includes the implantation of a cardioverter defibrillator regardless of the etiology; results of genetic testing do not change treatment. At this time, the clinical utility of genetic testing for SQTS has not been established.

Professional Society/Organizations
American College of Cardiology (ACC) /American Heart Association (AHA) Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (HRS) (2017): on behalf on the ACC/AHA/HRS, Al-Khatib et al., noted the availability of genetic testing for inherited arrhythmia syndromes can:

- provide opportunity to confirm a suspected clinical diagnosis and sometimes provide prognostic information for the proband
- offer cascade screening of potentially affected family members when a disease-causing mutation is identified in the proband.
- The yield of genetic testing varies by disease

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) (2011): On behalf of the HRS/EHRA, Ackerman et al. (2011) published an expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Regarding SQTS, the statement notes:

- Comprehensive or SQT1-3 (*KCNH2*, *KCNQ1*, and *KCNJ2*) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype. (Class IIb-May be Useful)
- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case. (Class I-Is recommended)

Left Ventricular Noncompaction Cardiomyopathy (LVNC): Left ventricular noncompaction is a cardiac muscle disorder that occurs when the left ventricle, which helps the heart pump blood, does not develop correctly. Instead of the muscle being smooth and firm, it is thick, appears spongy, is weak, and has an impaired ability to pump blood because it either cannot completely contract or it cannot completely relax. Some individuals with left ventricular noncompaction experience no symptoms at all, while others experience signs and symptoms including: abnormal blood clots, arrhythmia, palpitations, extreme fatigue during exercise, shortness of breath, syncope, lymphedema, and trouble laying down flat. Diagnosis can occur at any age, from birth to late adulthood. Approximately two-thirds of individuals with left ventricular noncompaction develop heart failure.

Mutations in several genes have been found to cause left ventricular noncompaction. Variants in the MYH7 and MYBPC3 genes have been estimated to cause up to 30 percent of cases; variants in other genes are each responsible for a small percentage of cases. However, the cause of the condition is often unknown. It is unclear how genetic variants cause left ventricular noncompaction. Normally, during development before birth, cardiac muscle gets condensed (compacted), becoming smooth and firm. Variants in certain genes likely lead to changes in this process. As a result, the left ventricular cardiac muscle is not compacted but is thick and spongy, leading to left ventricular noncompaction. van Waning et al. (2019) published a systematic review of genotype-phenotype correlations in noncompaction cardiomyopathy. In adult patients, the main causes were single missense mutations in sarcomere genes, while children more frequently had an X-linked or mitochondrial inherited defect (P=0.001) or chromosomal

anomalies (P<0.001). MYH7 was involved in 48% of the sarcomere gene mutations. MYH7 and ACTC1 mutations had lower risk for major adverse cardiac events than MYBPC3 and TTN (P=0.001). The noncompaction cardiomyopathy/dilated cardiomyopathy cardiac phenotype was the most frequent subtype (56%; P=0.022) and was associated with an increased risk for major adverse cardiac events and high risk for left ventricular systolic dysfunction (<0.001). Most of the included studies were case reports or small case series. There is insufficient evidence in the published peer-reviewed scientific literature regarding the clinical utility of genetic testing for left ventricular noncompaction cardiomyopathy.

Professional Society/Organizations
Heart Failure Society of America ([HFSA], 2018): On behalf of the HFSA, Hershberger et al. (2018) published a practice guideline regarding the Genetic Evaluation of Cardiomyopathy. The guideline notes in contrast to HCM, DCM, RCM and ARVC, LVNC remains without a consensus whether or not it should be considered a primary cardiomyopathy or a phenotype; however, the designation of a phenotype is favored by the HRS. LVNC may be present in 2-10% of the population and may also progress and regress. LVNC may be observed in conjunction with other cardiomyopathy phenotypes, and if so, recommendations for that cardiomyopathy derive clinical screening recommendations. Because of the high prevalence of the LVNC phenotype in otherwise normal individuals in population-based studies and limited evidence of disease causation from the LVNC phenotype itself, no recommendations are provided regarding family-based phenotype screening of LVNC that is not accompanied by other cardiovascular phenotypes with known disease risks.

Heart Rhythm Society ([HRS], 2019): In collaboration with, and endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the American Society of Echocardiography (ASE), the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Failure Society of America (HFSA), the International Society for Heart & Lung Transplantation (ISHLT), the Japanese Heart Rhythm Society (JHRS), the Latin American Heart Rhythm Society (LAHRS), the National Society of Genetic Counselors (NSGC), the Pediatric & Congenital Electrophysiology Society (PACES), and the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC), Towbin et al. published an expert consensus statement on the evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy, which includes LVNC.

Regarding genetic testing for LVNC the consensus statement notes in individuals with the clinical diagnosis of pathologic LVNC, genetic counseling and genetic testing are reasonable for diagnosis and for gene-specific targeted cascade family screening (Class of evidence [COR IIa; moderate strength of evidence], Level of evidence [LOE B-NR: Moderate strength of evidence [moderate, non-randomized]).

Polygenic risk score testing: A polygenic risk score is an estimate of an individual's genetic risk for a specific polygenic phenotype that is derived from weights of alleles from hundreds to thousands of loci. A polygenic risk score informs about an individual's relative risk compared to the remainder of the population. Published peer-reviewed scientific literature for polygenic risk scores is lacking and insufficient to support coverage.

Genetic Testing (Screening) in the General Population: The clinical utility of genetic testing in the general population for familial cardiac conditions is unknown and the role of such testing has not been established. Rather, confirmatory testing for affected individuals and predictive testing for at-risk individuals may assist in establishing a plan for monitoring or other targeted treatment if a specific variant has been identified.

Professional Society/Organizations
Support for genetic screening for inherited cardiomyopathies and arrhythmias in the general

population and for the use of multi-condition is lacking in the form of published professional society/organizational consensus guidelines.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No NCD found	
LCD	Local	No LCD found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination).

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A

CPT®* Codes	Description
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
81479†	Unlisted molecular pathology procedure
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

†**Note: Considered Medically Necessary when used to report any genetic testing for hereditary cardiomyopathy and/or arrhythmia that does not have an assigned CPT or HCPCS code**

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

Considered Not Medically Necessary:

CPT®* Codes	Description
0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81479††	Unlisted molecular pathology procedure

††**Note: Considered Not Medically Necessary when used to report genetic testing for atrial fibrillation, short QT syndrome and left ventricular noncompaction cardiomyopathy (LVNC)**

References

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Revision Details

Type of Revision	Summary of Changes	Date
Annual	Updated verbiage related to genetic counseling	3/15/2024