Corporate Medical Policy

Genetic Testing for Inherited Cardiomyopathies and Channelopathies AHS – M2025

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Description of Procedure or Service

Cardiomyopathies are diseases of the heart muscle. These conditions are frequently genetic and do not include muscle abnormalities caused by coronary artery disease, hypertension, valvular disease, and congenital heart disease. Symptoms include arrhythmia, cardiac dysfunction, and heart failure (Cooper, 2019).

Channelopathies, also known as primary electrical disease, are a group of cardiac diseases caused by genetic defects in ion channels of the heart leading to arrhythmias, syncope and the risk of sudden cardiac death (SCD) (Campuzano, Sarquella-Brugada, Brugada, & Brugada, 2015).

Related Policies
Cardiovascular Disease Risk Assessment AHS – G2050

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

Policy

BCBSNC will provide coverage for genetic testing for cardiomyopathies and channelopathies when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

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

When Genetic Testing for Cardiac Ion Channelopathies is covered

1. Reimbursement for genetic counseling for genetic testing for inherited cardiomyopathies and channelopathies is allowed. Genetic counseling is required for individuals prior to and after undergoing genetic testing for inherited cardiomyopathies and channelopathies for diagnostic, carrier, and/or risk assessment purposes.

2. Sequencing of LQTS-associated genes, is considered medically necessary for:

    a. Symptomatic individuals, (defined as a syncopal event) with a Schwartz score > 1

OR

b. Asymptomatic individuals with a first-, second-, or third-degree relative with confirmed LQTS and in whom the familial mutation is not known

3. Testing for a known familial mutation is considered medically necessary for first-, second, and third-degree relatives of an individual with a documented LQTS-causing mutation, even silent carriers.

4. Genetic testing for LQTS with duplication/deletion analysis is considered medically necessary if sequence analysis is negative, and the clinical suspicion of congenital LQTS remains high, based on a Schwartz score > 1.

5. Genetic testing for CPVT is considered medically necessary in the following situations:
   a. A close relative (i.e., first-, second-, or third-degree relative) with a known CPVT mutation; or

   b. A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable; or

   c. Signs and/or symptoms indicating a moderate-to-high pretest probability of CPVT, but a definitive diagnosis cannot be made without genetic testing.

   d. Persons who display exercise-, catecholamine-, or emotion-induced PVT or ventricular fibrillation, occurring in a structurally normal heart

6. Genetic testing for Brugada syndrome is considered medically necessary in the following situations:
   a. When signs and/or symptoms consistent with Brugada Syndrome are present, but a definitive diagnosis cannot be made without genetic testing.

   b. Patients have a close relative (ie, first-, second-, or third-degree relative) with a known Brugada Syndrome mutation.

7. Genetic testing for Short QT Syndrome is considered medically necessary in patients with a close relative (ie, first-, second-, or third-degree relative) with known SQTS mutation.

8. Genetic testing for dilated cardiomyopathy is considered medically necessary for patients with dilated cardiomyopathy and significant cardiac conduction disease (i.e. first-, second, or third-degree heart block) and/or have one or more family members who experienced sudden cardiac death or developed unexplained heart failure before age 60.

9. Genetic testing for a known familial mutation associated with dilated cardiomyopathy is considered medically necessary in asymptomatic close relatives (i.e. first-, second-, or third-degree relative) of a proband.

10. Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) is considered medically necessary in the following situations:

a. When signs and/or symptoms consistent with ARVC are present, but a definitive diagnosis cannot be made without genetic testing.

b. Patients have a close relative (ie, first-, second-, or third-degree relative) with a known ARVC mutation.

11. Genetic testing for a known familial mutation associated with progressive cardiac conduction disease (CCD or Lev-Lenegre disease) is considered medically necessary in asymptomatic close relatives (i.e. first-, second-, or third-degree relative) of a proband.

12. Genetic testing for a known familial mutation associated with restrictive cardiomyopathy (RCM) is considered medically necessary in asymptomatic close relatives (i.e. first-, second-, or third-degree relative) of a proband.

13. Genetic testing for left ventricular noncompaction (LVNC) is considered medically necessary in the following situations:
    a. When signs and/or symptoms consistent with LVNC are present, but a definitive diagnosis cannot be made without genetic testing.

    b. Patients have a close relative (ie, first-, second-, or third-degree relative) with a known LVNC mutation.

14. Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered medically necessary for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene mutation present in that affected relative.

When Genetic Testing for Cardiac Ion Channelopathies is not covered

Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) is considered not medically necessary for patients who meet the diagnostic criteria for HCM in order to facilitate cascade screening of their first-degree relatives.

Genetic testing for predisposition to HCM is considered not medically necessary for patients with a family history of HCM in which a first-degree relative with HCM has tested negative for pathologic mutations.

Genetic testing for LQTS is considered not medically necessary for symptomatic individuals with a Schwartz score ≤1.

Genetic testing for LQTS to determine prognosis and/or direct therapy in patients with known LQTS is considered investigational.

Genetic testing for LQTS or CPVT is considered investigational for all other situations when the above criteria are not met.

Genetic testing for Brugada Syndrome for all other situations not meeting the criteria outlined above is considered investigational.

Genetic testing for SQTS for all other situations not meeting the criteria outlined above is considered investigational.

Genetic testing for Early Repolarization "J-wave" Syndrome, Sinus Node Dysfunction (SND) and/or other rhythm disorders is considered investigational.

Genetic testing for predisposition to HCM is considered investigational for all other patient populations, including but not limited to individuals who have a first-degree relative with clinical HCM, but in whom genetic testing is unavailable.

Policy Guidelines

Background

Cardiomyopathies
In 1995, the WHO divided cardiomyopathies into five categories; dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), and unclassified cardiomyopathies. Cardiomyopathies have a variety of genotypes and phenotypes that typically require echocardiographic evaluation. Either phase of the heartbeat (systole or diastole) may be affected (Cooper, 2019).

Systolic dysfunction is usually characterized by a decrease in myocardial contractility. This decrease causes a reduction in the ejection fraction of the left ventricle (LV), thereby forcing one of two compensatory mechanisms; either the LV itself increases in size (leading to larger stroke volume) or the contractility of the heart increases in response to increased stretch. However, these compensatory mechanisms will eventually fail, leading to physiological manifestations of heart failure. This dysfunction is often seen in DCM, as well as some HCM patients (Cooper, 2019).

Diastolic dysfunction refers to abnormal LV relaxation and filling, as well as elevated filling pressures. As with systolic dysfunction, the primary issue with diastole is caused by abnormal contractility of the heart muscle. The contractility of the myocardium influences both the LV relaxation phase (the isovolumetric period between the aortic valve's close and mitral valve's opening) and passive compliance phase (variable pressure, starting at mitral valve's opening) of diastole. Due to the impaired contractility of the myocardium, the pressure in each phase is abnormal. Dysfunction in this phase is often seen in HCM, RCM, and DCM (Cooper, 2019).

Hypertrophic cardiomyopathy (HCM)
Hypertrophic cardiomyopathy (HCM) is a commonly inherited cardiovascular disease defined as thickening of the ventricular wall resulting from more than 1500 mutations in 11 or more genes encoding proteins of the cardiac sarcomere (M. Maron, 2019).

HCM is characterized by left ventricular hypertrophy (LVH, thickness of ≥15 mm), observed by echocardiography or magnetic resonance imaging and not otherwise explainable by other cardiovascular issues, such as coronary artery disease, hypertension, valvular disease, and congenital heart disease. Development of LVH usually starts in adolescence and is complete by early adulthood. Symptoms include chest pain, dyspnea and syncope, and severe disease can lead to disabling complications, including heart failure and malignant ventricular arrhythmias. However, many patients with HCM are asymptomatic or have minimal symptoms and are only discovered through means such as family screenings or an abnormal ECG (M. Maron, 2019). HCM is the most frequent cause of sudden death in young people and can lead to functional disability from heart failure and stroke (B. J. Maron, 2003). HCM is a relatively common finding with a prevalence of approximately 1 in 500 people (B. J. Maron et al., 1995). However, estimates of clinically expressed HCM plus gene carriers are as high as 1 in 200 (Semsarian, Ingles, Maron, & Maron, 2015).

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

Wide phenotypic variability exists, ranging from asymptomatic to severe life-threatening heart failure even within the same mutation. This variability in clinical expression may be related to environmental factors and modifier genes (Alcalai, Seidman, & Seidman, 2008). Moreover, no strong correlation between left ventricular problems and symptoms exist; patients with major obstructions or hypertrophy may be asymptomatic and vice versa. The primary characteristic of LVH is present in multiple conditions, such as systemic hypertension, Fabry disease, aortic stenosis, and more. Such conditions should be excluded before a diagnosis of HCM is made (M. Maron, 2019).

Diagnostic screening of first-degree relatives is important to identify at risk patients. Guidelines have been established for clinically unaffected relatives of affected individuals. Clinical screening with physical examination, electrocardiography, and echocardiography is recommended every 12 to 18 months for individuals between the ages of 12 to 18 years and every 3 to 5 years for adults with additional screening recommended for any change in symptoms (Gersh et al., 2011).

Dilated cardiomyopathy (DCM)
Dilated cardiomyopathy (DCM) is characterized by dilation and impaired contraction of one or both ventricles (Dec & Fuster, 1994). The dilation often becomes severe and is invariably accompanied by an increase in total cardiac mass. Affected patients have impaired systolic function and clinical presentation is usually with features of heart failure (Cooper, 2019).

Dilated cardiomyopathy is caused by a variety of disorders. The cause is unknown for over 50% of patients with the disease. Familial dilated cardiomyopathy is caused by a genetic mutation in 20-35% with the disease. DCM is transmitted primarily in an autosomal dominant inheritance pattern. Mutations in over 30 genes have been determined to cause familial dilated cardiomyopathy (Hershberger, 2017).

Other common causes for DCM include (AHA, 2016) coronary heart disease, heart attack, high blood pressure, diabetes, thyroid disease, viral hepatitis and HIV, infections, especially viral infections that inflame the heart muscle, alcohol, complications during the last month of pregnancy or within 5 months of birth, certain toxins such as cobalt, certain drugs (such as cocaine and amphetamines) and two medicines used to treat cancer (doxorubicin and daunorubicin).

Genetic forms of dilated cardiomyopathy are diagnosed by family history and molecular testing. Genes associated with familial dilated cardiomyopathy include *MYH7, MYBPC3, TNNT2, TNNC1, TNNI3, TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKG2,*

LAMP2, *GLA*, *LMNA*, *BAG3*, *RBM20*, *SCN5A*, *DES*, *DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, *RYR2*, *TMEM43*, and *TTN* (Hershberger et al., 2018).

Notably, the frequencies of DCM mutations in any one gene are low (<<1% to 6-8%), and a genetic cause is identified in only 30-35% of familial DCM cases. Therefore, routine genetic testing for DCM was only recommended in familial disease (≥2 affected family members) (Yancy et al., 2013). However, as molecular genetic testing laboratories offer DCM genetic testing panels of 12-30 genes utilizing next generation sequencing methods, testing sensitivity now ranges from 15-25%, has become standard of care (M. J. Ackerman et al., 2011; Hershberger, 2017; Hershberger et al., 2009; Hershberger, Morales, & Siegfried, 2010; Hershberger & Siegfried, 2011).

Guidelines now recommend testing for all patients with cardiomyopathy even if no other disease is evident in the family. Genetic testing is clinically useful in the management of affected individuals, as well as to assess risk in relatives (Hershberger et al., 2018). LMNA mutations are associated with high rates of conduction system disease, ventricular arrhythmias, and sudden cardiac death (SCD), and may consequently lower the threshold for prophylactic ICD implantation. DCM patients with a variant of the SCN5A gene exhibit a phenotype associated with significant arrhythmias and frequent premature ventricular complexes. Although such patients responded poorly to conventional HF therapy, treatment with sodium channel blocking drugs produced a dramatic reduction in ectopy and normalization of left ventricular (LV) function." (Japp, Gulati, Cook, Cowie, & Prasad, 2016)

Restrictive cardiomyopathy (RCM)
RCM differs from other cardiomyopathies in that there may not be many physical abnormalities (i.e. no dilation or hypertrophy). However, the ventricular filling process is still significantly impaired. RCM may be difficult to see on two-dimensional imaging, and assessment of flow velocity across the mitral valve is more accurate in detecting these filling abnormalities (Cooper, 2017). Some cases of RCM are secondary to a more apparent cardiac condition. However, idiopathic cases of RCM are generally genetic conditions. Pathogenic mutations in sarcomeric or cytoskeletal genes such as TNNI3, TNNT2, and TPN1 have been linked to familial RCM (Ammash, 2018).

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
ARVC is characterized by changes in myocardium of the right (and often left as well) ventricular free wall. This myocardium is replaced by fibrous or fibro-fatty tissue, causing dysfunction of the affected ventricles (Cooper, 2019). At the molecular level, the desmosomes are typically impaired due to genetic mutations. This causes the mechanical stress of the heart to detach myocytes, which eventually leads to their death. The initial repair mechanisms of this detachment are what produces the fibrous tissue. Up to 30% of ARVC cases are familial, and mutations in gene products such as plakoglobin and desmoplakin have been associated with ARVC (McKenna, 2017).

Unclassified Cardiomyopathies
Other types of cardiomyopathy that do not fall into one of the other four categories are considered "unclassified". For example, left ventricular noncompaction (LVNC) falls in this category due to its characteristic myocardial wall; the myocardial wall consists of "prominent trabeculae and deep intertrabecular recesses", thereby resulting in two layers of myocardium of different thickness. This condition may be sporadic or familial; up to 50% of LVNC cases are familial. Genes such as alpha-dystrobrevin or other sarcomeric genes may contribute to LVNC (Attenhofer-Jost, 2019).

This category also includes cardiomyopathies such as stress-induced cardiomyopathy and cirrhotic cardiomyopathy (Cooper, 2019).

Clinical Validity and Utility

A recent study by Cirino et al compared the results from panel genetic testing to whole genome sequencing (WGS). Forty-one patients with HCM who had undergone targeted genetic testing (either multigene panel or familial variant test) were recruited into a clinical trial of WGS. Panel size ranged from 4-62 genes, and all but two subjects were tested for the main eight sarcomeric genes (MYH7, MYBPC3, TNNT2, TPM1, MYL2, MYL3, TNNI3, ACTC). The authors stated that WGS detected nearly all variants identified on panel testing and allowed further analysis of posited disease genes. Several variants of uncertain clinical use and other genetic findings were also identified. Panel testing and WGS provided similar results, but WGS provides reanalysis over time; however, WGS also requires genomic expertise to correctly interpret results (A. L. Cirino et al., 2017).

A study focusing on the non-sarcomeric genes contributing to HCM was performed by Walsh et al. A reference sample of 60,706 exomes were analyzed and compared to 6,179 HCM cases. This comparison revealed a large amount of gene variants in the main eight sarcomeric genes (MYH7, MYBPC3, TNNT2, TPM1, MYL2, MYL3, TNNI3, ACTC1) but very few variants of the non-sarcomeric genes in HCM cases. The authors concluded the variation in most of the non-sarcomeric genes does not affect HCM significantly as 99% of HCM pathogenic variants were found to be in the main eight sarcomeric genes. Four non-sarcomeric genes were found to have an excess of variants, but even these amounted to only 2% of the HCM cases overall; the other 26 non-sarcomeric genes examined were found to have very little or no excess variation over the reference sample of exomes. Furthermore, the authors state that only the well-known variants are symptomatic whereas the other variants are of unknown significance or benign, making clinical sequencing of limited use. The authors recommended that the only genes tested should be the eight sarcomeric genes, the metabolic cardiomyopathy genes, and possibly ACTN2 and MYOZ2 (Walsh et al., 2017).

Bhonsale et al assessed the impact of genotype on clinical outcomes of ARVC patients. Pathogenic mutations were evaluated in 577 patients. The investigators found that patients with a desmoplakin-associated mutation had an over four-fold occurrence of left ventricular (LV) dysfunction and heart failure than PKP2 carriers. No significant difference was found between clinical outcomes of patients with missense mutations and patients with truncating or splice site mutations. Patients with multiple mutations had more severe symptoms, such as lower survival rate without ventricular fibrillation or tachycardia, more frequent LV dysfunction, heart failure, cardiac transplant, and earlier occurrence of sustained ventricular fibrillation and tachycardia, as compared to those with only one mutation (Bhonsale et al., 2015).

Kostareva and colleagues evaluated the “genetic spectrum” of idiopathic RCM. The authors screened for 108 cardiomyopathy and arrhythmia-associated genes in 24 patients with idiopathic RCM. They found pathogenic and “likely-pathogenic” variants in 13 of the 24 patients (54%), and half of these genotype-positive patients carried a combination of pathogenic variants, likely-pathogenic variants, and variants of unknown significance. The most frequent combination included mutations in sarcomeric and cytoskeletal genes (Kostareva et al., 2016).

Kayvanpour et al evaluated the genetic-phenotype associations for DCM. 48 studies encompassing 8097 patients were included, and the authors investigated mutations in LMNA, PLN, RBM20, MYBPC3, MYH7, TNNT2 and TNNI3. The authors results were as follows: “The average frequency of mutations in the investigated genes was between 1 and 5 %. The mean age of DCM onset was the beginning of the fifth decade for all genes. Heart transplantation (HTx) rate was highest in LMNA mutation carriers (27 %), while RBM20

mutation carriers were transplanted at a markedly younger age (mean 28.5 years). While 73 % of DCM patients with LMNA mutations showed cardiac conduction diseases, low voltage was the reported ECG hallmark in PLN mutation carriers. The frequency of ventricular arrhythmia in DCM patients with LMNA (50 %) and PLN (43 %) mutations was significantly higher. The penetrance of DCM phenotype in subjects with TTN truncating variants increased with age and reached 100 % by age of 70" (Kayvanpour et al., 2017).

Cardiac Ion Channelopathies

The electromechanical pumping action of the heart maintains circulation and ensures the delivery of blood and nutrients to all organs to support their normal function. Synchronized contraction of the myocardium is necessary to generate sufficient pressure to drive blood flow (Voorhees & Han, 2015). Mechanical contraction of cardiac myocytes is coordinated by the generation and propagation of an action potential (Fernandez-Falgueras, Sarquella-Brugada, Brugada, Brugada, & Campuzano, 2017) through the synergistic activation and inactivation of several voltage-dependent ion channels. Membrane depolarization during the action potential leads to the opening of the voltage-gated calcium channels resulting in an inward current, followed by the efflux of potassium ions, generation of an outward current, and cell repolarization (Garcia-Elias & Benito, 2018). Action potential duration is determined by the magnitude and timing of inward and outward currents (Kirk & Kass, 2015). Differential expression, selectivity and gating properties of cardiac ion channels in distinct regions of the heart promote unidirectional propagation of electrical activity (Fernandez-Falgueras et al., 2017).

Mutations in genes encoding these specific channels or associated proteins may impair ionic conduction resulting in changes in action potential, synchronization, and/or propagation of electrical impulse and predispose to potentially malignant arrhythmias (Nerbonne & Kass, 2005; Roden, Balser, George, & Anderson, 2002). Dyssynchronous contraction of the ventricle, arising from electrical activation delays, also significantly worsens morbidity and mortality in heart failure (HF) patients (Kirk & Kass, 2015). Ion channelopathies have been identified as a significant cause of sudden cardiac death (SCD) in patients with structurally normal hearts(Campuzano et al., 2015; Magi, Lariccia, Maiolino, Amoroso, & Gratteri, 2017), and some cases of otherwise unexplained stillbirth (Munroe et al., 2018).

Patients can show early symptoms of palpitations or hemodynamic compromise, including dizziness, seizure, or syncope, particularly following exertion, however in many cases SCD is the only sign of cardiac trouble (Martin, Huang, & Matthews, 2013). Electrical disturbances in the heart rhythm that can be detected on electrocardiogram (ECG) of some patients with channelopathies result in diagnosis of:

- Long QT Syndrome (LQTS), characterized by prolonged ventricular repolarization and electrocardiographic prolongation of the QT interval (QTc $\geq$ 480 ms in repeated 12-lead ECG, although a QTc $\geq$ 460 ms is sufficient in the presence of unexplained syncope). The variable clinical manifestations of LQTS range from asymptomatic patients diagnosed through family screening, to SCD, syncope, convulsions, malignant ventricular arrhythmias, VF, and *torsade de pointes* (Fernandez-Falgueras et al., 2017). The prevalence of LQTS in infants is approximately to 1/2000 (Schwartz et al., 2009).
- Brugada Syndrome (BrS) is clinically characterized by right ventricular conduction delay and ST-segment elevation in the anterior right precordial leads. Syncope is one of the main clinical manifestations; individuals with BrS develop a monomorphic ventricular tachycardia that may precipitate during sleep, rest or fever(Magi et al., 2017). Recent

reports suggest that BrS could be responsible for 4%–12% of all SD and up to 20% of SD in patients with structurally normal hearts (Fernandez-Falgueras et al., 2017).

- Short QT Syndrome (SQTS), is characterized by abnormally short QT intervals and an increased propensity to develop atrial and ventricular tachyarrhythmia in the absence of structural heart disease. Cardiac arrest seems to be the most frequent symptom (up to 40%). Palpitations are a common symptom (30%), followed by syncope (25%) and atrial fibrillation (AF), which are the first symptoms of the disease in up to 20% of patients. The episodes may occur in a wide range of situations such as in reaction to loud noise, at rest, during exercise, and during daily activity (Fernandez-Falgueras et al., 2017)
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), is characterized by a normal ECG and ventricular arrhythmia in genetically predisposed individuals during intense physical exercise or acute emotional stress. Typical clinical manifestations of CPVT include dizziness and syncope. However, ventricular arrhythmia may degenerate into rapid polymorphic ventricular tachycardia and ventricular fibrillation, leading to SCD(Magi et al., 2017).
- Progressive Cardiac Conduction Disease (CCD) is characterized by problems with the cardiac impulse of the heart. These conduction abnormalities may be accompanied by structural problems such as fibrous or fatty calcification, and an ECG may display unusual patterns such as a prolonged P-wave or prolonged QRS interval. These arrhythmias may lead to sudden cardiac death. Mutations in ion channel proteins such as TRPM4 or SCN5A have been associated with CCDs (M.J. Ackerman et al., 2011; Wilde, Veldkamp, & Smits, 2005).

Not all cases are accompanied by changes in ECG, which makes them more difficult to diagnose. Genetic testing can contribute substantially both to the diagnosis of affected patients and with the identification of asymptomatic individuals at risk (Bastiaenen & Behr, 2011; Priori et al., 2013).

Currently, mutations associated with SCD have been identified in sodium, potassium and calcium channels and associated proteins (Fernandez-Falgueras et al., 2017). A general overview of the main genetic variants that have been linked to the major cardiac channelopathies is displayed in the table below [adapted from (Garcia-Elias and Benito, 2018; Magi et al., 2017; Munroe et al., 2018; Tester and Ackerman, 2011)].

Gene	Protein	Prevalence	Other Associations
Brugada Syndrome (BrS)			
	Ion Channel Subunits		
*SCN5A**	NaV1.5 (α-subunit of the voltage-dependent Na^+channel)	≃25% (BrS1)	DCM, ARVC, Heart block, LQTS, S SIDS
*SCN1B**	β1-subunit of the voltage-dependent Na^+ channel	<1%	CCD, Epilepsy
*SCN2B**	β2-subunit of the voltage-dependent Na^+ channel	<1%	AF
*SCN3B**	β3-subunit of the voltage-dependent Na^+ channel	<1%	AF, VF, SIDS
*SCN10A**	NaV1.8 (α-subunit of the neuronal voltage-dependent Na^+ channel)	≃10%	LQTS, AF, painful small-fiber periph neuropathy

*CACNA1C**	CaV1.2 (α1C-subunit of the volatge-dependent L-type Ca^{2+} channel)	<1%	Timothy syndrome, LQTS
*CACNB2b**	β2-subunit of the voltage-dependent L-type Ca^{2+}channel	<1%	SQTS
*KCND3**	KV4.3 (α-subunit of the voltage-dependent K^+channel)	<1%	SIDS, Spinocerebellar ataxia
*KCNE3**	minK-related peptide 2 (β-subunit of the voltage-dependent K^+ channel)	<1%	
KCNAB2	β2-subunit of the voltage-dependent K^+ channel	<1%	
KCND2	KV4.2 (voltage-dependent K^+ channel)	<1%	Epilepsy
*KCNE5**	minK-related peptide 4 (β-subunit of the voltage-dependent K^+ channel)	<1%	AF, VF
*KCNJ8**	Kir6.1 (inward-rectifier K^+channel, subunit of the ATP-sensitive K^+ channel)	<1%	VF, SIDS, Cantu syndrome
*ABCC9**	SUR2 (sulfonylurea receptor, subunit of the ATP-sensitive K^+ channel)	<1%	DCM, ERS, Cantu syndrome and related disorders
*KCNH2**	KV11.1/hERG (α-subunit of the voltage-dependent K^+ channel)	<1%	LQTS, SQTS
*CACNA2D1**	α2/δ subunit of the volatge-dependent L-type Ca^{2+}channel	<1%	Epilepsy
*HCN4**	hyperpolarization-activated, cyclic nucleotide-gated ion channel 4	<1%	SSS, AF, AV block, Bradycardia, Tachycardia, NCC
*TRPM4**	Transient receptor potential melastatin 4	<1%	Herat Block, LQTS
	Auxillary Proteins		
FGF12	fibroblast growth factor 12	<1%	Epilepsy
*GPD1L**	glycerol-3-phosphate dehydrogenase 1-like	<1%	
SLMAP	sarcolemma associated protein (striatin-interacting phosphatase and kinase complex)	<1%	
*PKP2**	plakophillin-2	<1%	ARVC
SEMA3A	semaphorin-3A	<1%	
*RANGRF**	MOG1 (multicopy suppressor of *Gsp1*)	<1%	histiocytoid cardiomyopathy
HEY2	CHF1 (cardiovascular helix-loop-helix factor 1)	<1%	
Long QT Syndrome (LQTS)			
	Ion Channel Subunits		

*KCNQ1**	KV7.1 (α-subunit of the voltage-dependent K^+ channel)	≃40% (LQT1)	JLNS, SQTS
*KCNH2**	KV11.1/hERG (α-subunit of the voltage-dependent K^+channel)	≃30% (LQT2)	SQTS
*SCN5A**	NaV1.5 (α-subunit of the voltage-dependent Na^+ channel)	≃10% (LQT3)	BrS, DCM, ARVC, Heart block, SSS, SIDS
*KCNE1**	minK (β1-subunit of the voltage-dependent K^+ channel)	<1%	JLNS
*KCNE2**	MiRP1 (β2-subunit of the voltage-dependent K^+ channel)	<1%	
*KCNJ2**	Kir2.1 (inward rectifying K^+ channel)	<1% (LQT7)	Andersen-Tawil syndrome, SQTS, AF
*KCNJ5**	Kir3.4 (G protein-activated inward rectifying K^+ channel 4)	<1%	LQTS, Hyperaldosteronism
*SCN1B**	β1-subunit of the voltage-dependent Na^+ channel	<1%	BrS, CCD, Epilepsy
*SCN4B**	β4-subunit of the voltage-dependent Na^+ channel	<1%	AF
*CACNA1C**	CaV1.2 (α1C-subunit of the voltage-dependent L-type Ca^{2+} channel)	<1% (LQT8)	BrS, Timothy syndrome
	Auxillary Proteins		
*AKAP9**	A-kinase anchor protein-9	<1%	
*ANK2**	ankyrin B	<1%	Arrhythmia
*CALM1**	calmodulin (CaM)	<1%	CVPT
*CALM2**	calmodulin (CaM)	<1%	CVPT
*CALM3**	calmodulin (CaM)	<1%	CVPT
*SNTA1**	α1-syntrophin	<1%	
*TRDN**	triadin	<1%	CVPT
*CAV3**	caveolin-3	<1%	HCM, LGMD, Rippling muscle disease, Tateyama-type distal myopathy, SIDS
*TRPM4**	Transient receptor potential melastatin 4	<1%	Herat Block, BrS
*RYR2**	ryanodine receptor 2 (RyR2)	<1%	ARVC, CPVT
Short QT Syndrome (SQTS)			
	Ion Channel Subunits		
*KCNH2**	KV11.1/hERG (α-subunit of the voltage-dependent K^+ channel)	≃15% (SQT1)	LQTS
*KCNQ1**	KV7.1 (α-subunit of the voltage-dependent K^+channel)	<1%	JLNS, LQTS
*KCNJ2**	Kir2.1 (inward rectifying K^+ channel)	<1%	Andersen-Tawil syndrome, AF

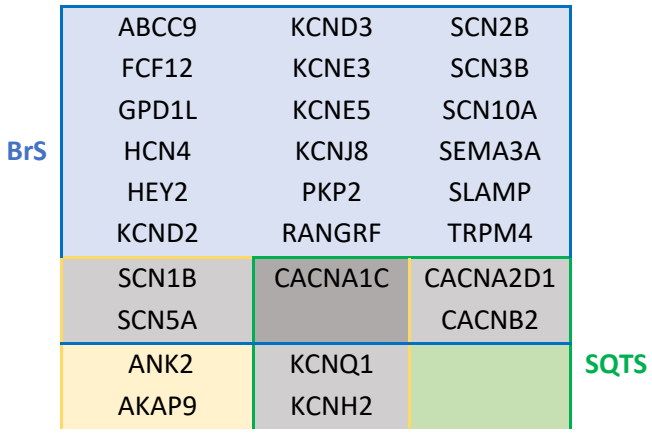
*CACNA1C**	CaV1.2 (α1C-subunit of the voltage-dependent L-type Ca^{2+} channel)	<1%	BrS, Timothy syndrome
*CACNB2b**	β2-subunit of the voltage-dependent L-type Ca^{2+}channel	<1%	BrS
*CACNA2D1**	α2/δ-subunit of the voltage-dependent L-type Ca^{2+} channel	<1%	BrS, Epilepsy
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)			
*RYR2**	ryanodine receptor 2 (RyR2)	≃50–60% (CPVT1)	ARVC
KCNJ2	Kir2.1	10%	
*CASQ2**	calsequestrin 2	≃5%	
*TRDN**	triadin	<1%	LQTS
*CALM1**	calmodulin (CaM)	<1%	LQTS
*CALM2**	calmodulin (CaM)	<1%	LQTS
*CALM3**	calmodulin (CaM)	<1%	LQTS
TECLR	trans-2,3-enoyl-CoA reductase-like	<1%	

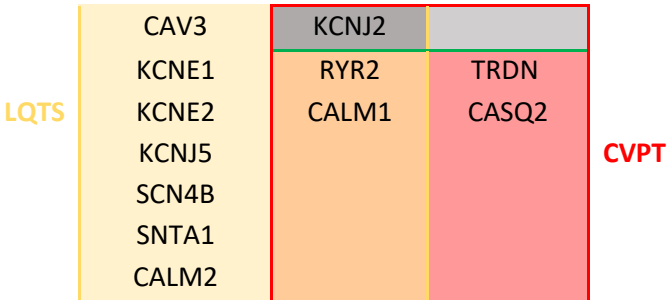
** - commercially available test*

Abbreviations: AF – Atrial fibrillation; ARVC- Arrhythmogenic right ventricular cardiomyopathy; AV – Atrioventricular; BrS – Brugada syndrome; CCD – Cardiac conduction defect; CHD – Congenital heart defects; CPVT –Catecholaminergic polymorphic ventricular tachycardia; DCM – Dilated cardiomyopathy; EMD – Emery Dreifuss muscular dystrophy; ERS –Early repolarization syndrome; HCM – Hypertrophic cardiomyopathy; HCC - histiocytoid cardiomyopathy; JLNS – Jervell and Lange-Nielsen syndrome; LGMD – Limb girdle muscular dystrophy; LQTS – Long QT syndrome; SIDS – Sudden infant death syndrome; SQTS – Short QT syndrome; SSS – Sick sinus syndrome; SUDS – Sudden unexpected death syndrome; VF – Ventricular fibrillation

The clinical presentations of these conditions overlap as shown below (adapted from Campuzano, 2015), and genetic testing may clarify diagnoses, etiologies, and treatments in symptomatic individuals (Spoonamore & Johnson, 2016). However, predicting clinical presentation based on genetic mutation is also challenging (Bezzina, Lahrouchi, & Priori, 2015) due to the incomplete penetrance of most of these genes (Giudicessi & Ackerman, 2013).

Gene Mutations and their Associated Conditions





Several proprietary gene panels exist for the assessment of cardiac ion channelopathies. For example, GeneDX offers several customizable panels for various channelopathies and cardiomyopathies. Conditions such as ARVC, Brugada Syndrome, and CPVT are available as separate panels, and GeneDX offers combined panels such as a "Custom Arrhythmia Panel", a "Custom Cardiomyopathy Panel", and a "Combined Cardiac Panel" (GeneDX, 2018). Other commercially available panels include offerings from Invitae (Invitae), Fulgent, (Fulgent, 2020) and BluePrint Genetics (BluePrint, 2020)

Ware et al compared two NGS approaches for diagnostic sequencing inherited arrhythmia syndromes. PCR-based target enrichment and long-read sequencing (PCR-LR) was compared to in-solution hybridization-based enrichment and short-read sequencing (Hyb-SR). The PCR-LR assay comprehensively assessed five long-QT genes (KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2) and "hot spots" in RYR2. The Hyb-SR assay targeted 49 genes, including those in the PCR-LR assay. The sensitivity for detection of control variants was identical. In both assays, the major limitation was upstream target capture, particularly in regions of extreme GC content. These initial experiences with NGS cardiovascular diagnostics achieved up to 89% sensitivity at a fraction of current costs (Ware et al., 2013).

Proost et al (2017) validated a targeted gene panel for next-generation sequencing of 51 genes associated with primary electrical disease with 20 Human Polymorphism Study Center samples and 19 positive control samples with a total of 1479 variants. "An analytical sensitivity and specificity of 100% and 99.9% were obtained". After validation, the assay was applied to "114 PED patients which identified 107 variants in 36 different genes, 18 of which were classified as pathogenic or likely pathogenic, 54 variants were of unknown significance, and 35 were classified as likely benign". They concluded "that the PED Multiplex Amplification of Specific Targets for Resequencing Plus assay is a proficient and highly reliable test to routinely screen patients experiencing primary arrhythmias (Proost et al., 2017)."

Clinical Validity and Utility

Garcia et al proposed a framework for establishing clinical validity for assessing polymorphisms of inherited cardiac conditions, as well as evaluating the strength of association between genotype and phenotype, from a logical argument. Clinical validity of a gene is established when a gene is known to cause disease; since a specific variant must be responsible for causing the disease, a gene variant must be known to cause that disease. Conversely, if no variants can be established to cause disease, the clinical validity association has not been established. Variants of unknown significance (VUS) would, therefore, not have established clinical validity. Garcia et al proposed three categories of strength of association: strong, suggested, and emerging.

- "Strong" refers to "cases where there exists at least one clinically observed variant supported by sufficient evidence to classify that variant as pathogenic. "Strong" indicates that the relationship has been proven".
- "Suggested" is used in cases where some preliminary evidence exists suggesting a causal relationship, but the relationship has not yet been formally proven."
- "Emerging" is used to describe a growing suspicion that a specific condition is caused by a gene that has already been proven to cause disease.

The authors go on to state that as long as one "strong" relationship exists, then clinical validity has been established. If not, the gene should be considered of "uncertain significance" (Garcia et al., 2016).

The authors also provide recommendations for gene panels to test for certain conditions. They "propose that a comprehensive panel test designed for the molecular diagnosis of a particular condition should include the following classes of genes:

- Genes that have been conclusively proven to cause the condition in question.
- Genes suspected but not yet proven to cause the condition in question.
- Genes that have been conclusively proven to cause a condition within the clinical differential. This category should include genes that cause a condition that can progress into the condition in question, genes that cause a condition that can be confused with the condition in question, and genes that cause a syndrome that include the condition in question as a primary feature.

They suggest that the clinical validity of a panel is established when that panel includes a set of genes that account for a substantial proportion of the genetic causes of the disease in question. Conversely, a panel is NOT valid if it omits certain genes that account for a substantial proportion of the known genetic risk. A clinically valid panel may also include genes for which some preliminary evidence of clinical validity exists ("preliminary evidence genes") (Garcia et al., 2016).

Hofman et al (2013) analyzed the yield of DNA testing over 15 years. They analyzed results from 7021 individuals who were counseled, 6944 from 2298 different families (aged 41±19 years; 49% male). In 702 families (31%), a possible disease-causing mutation was detected. The yield of DNA testing of probands with primary electric diseases was 47% in LQTS, 26% in BrS, and 37% in CPVT. Cascade screening revealed 1539 mutation-positive subjects, and in 372 families counseled after sudden unexplained death an inherited arrhythmia syndrome was diagnosed in 29% (n=108) (Hofman et al., 2013).

Le Scouarnec (2015) et al examined 167 index cases presenting with a Brugada pattern on the electrocardiogram as well as 167 individuals aged over 65-years old and showing no history of cardiac arrhythmia. They found that "a significant enrichment in rare coding variation (with a minor allele frequency below 0.1%) was observed only for SCN5A, with rare coding variants carried by 20.4% of cases with BrS versus 2.4% of control individuals. No significant enrichment was observed for any other arrhythmia-susceptibility gene, including SCN10A and CACNA1C. These results indicate that, except for SCN5A, rarecoding variation in previously reported arrhythmia-susceptibility genes do not contribute significantly to the occurrence of BrS in a population with European ancestry. Extreme caution should thus be taken when interpreting genetic variation in molecular diagnostic setting, since rarecoding variants were observed in a similar extent among cases versus controls, for most previously reported BrS-susceptibility genes (Le Scouarnec et al., 2015)."

Tester et al (2012) examined 173 cases of sudden unexplained death that were referred for cardiac channel molecular autopsy. The mutational analysis included the long QT syndrome

genes (KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2) and a catecholaminergic polymorphic ventricular tachycardia (CPVT) type 1–associated gene (RYR2). Overall, 45 putative pathogenic mutations absent in 400 to 700 controls were identified in 45 autopsy-negative SUD cases (26.0%) (Tester et al., 2012).

Seidelmann et al (2017) evaluated the use of whole exome sequencing for clinical diagnosis, risk stratification, and management of inherited CVD. They found that genetic diagnosis was reached with a success rate of 26.5% (53/200 patients). This compares to 18% (36/200) that would have been diagnosed using commercially available genetic panels; although, this finding was not statistically significant. The authors concluded, "Whole exome sequencing was particularly useful for clinical diagnosis in patients with aborted sudden cardiac death, in whom the primary insult for the presence of both depressed cardiac function and prolonged QT had remained unknown. The analysis of the remaining cases using genome annotation and disease segregation led to the discovery of novel candidate genes in another 14% of the cases (Seidelmann et al., 2017)."

Munroe et al (2018) examined tissue from 242 stillbirths (≥22 weeks), including those where no definite cause of death could be confirmed after a full autopsy. 70 cases were examined, which were then sequenced for a custom panel of 35 genes. 1 putative pathogenic variant was found, and several novel variants of uncertain significance resulting in cardiac channelopathies was identified in some cases of otherwise unexplained stillbirth. The authors concluded "these variants may have a role in fetal demise (Munroe et al., 2018)."

Wang et al examined the "genetic spectrum" of LVNC. The authors sequenced 73 cardiomyopathy-related genes in 102 patients, and 43 pathogenic variants were identified in 16 genes in 39 patients. Sarcomeric variants accounted for 63% of these variants whereas variants associated with channelopathies accounted for 12%. MYH7 and TAZ pathogenic variants were the most common, and patients with pathogenic variants showed more severe symptoms such as earlier age of onset (Wang et al., 2017).

Van Lint et al evaluated the detection rates for variants of unknown (class 3), likely (class 4), and certain (class 5) pathogenicity in cardiogenetic gene panels. 936 patients were evaluated with the arrhythmia panels (4 versions), and 1970 patients were evaluated with the cardiomyopathy panels (6 versions). The arrhythmia panels detected class 3 variants in 34.8% of patients, class 4 variants in 4.2% of patients, and class 5 variants in 4.6% of patients. The cardiomyopathy panels detected class 3 variants in 40.8% of patients, class 4 variants in 7.9% of patients, and class 5 variants in 12% of patients. Overall, the arrhythmia panels detected variants of interest in 44% of patients, and the cardiomyopathy panels detected variants of interest in 61% of patients. The authors concluded that "larger gene panels can increase the detection rate of likely pathogenic and pathogenic variants, but mainly increase the frequency of variants of unknown pathogenicity" (van Lint et al., 2019).

Guidelines and Recommendations

American Heart Association, American College of Cardiology, and the Heart Rhythm Society

In 2017 (Al-Khatib Sana et al., 2018) the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) published the Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death that recommends the following:

Genetic Considerations in Arrhythmia Syndromes

- In patients and family members in whom genetic testing for risk stratification for SCA or SCD is recommended, genetic counseling is beneficial. (I)
- The diagnosis of most inherited arrhythmia syndromes is based on clinical features and family history. The availability of genetic testing for inherited arrhythmia syndromes can: 1) provide opportunity to confirm a suspected clinical diagnosis and sometimes provide prognostic information for the proband and 2) 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.
- Genotyping is frequently most useful when a pathogenic mutation is identified in the proband, such that screening can be applied to relatives who are in a preclinical phase, allowing institution of lifestyle changes, therapy, or ongoing monitoring for those who are gene mutation positive
- In young patients (<40 years of age) without structural heart disease who have unexplained cardiac arrest, unexplained near drowning, or recurrent exertional syncope, genetic testing may be important to identify an inherited arrhythmia syndrome as a likely cause.

Arrhythmogenic Right Ventricular Cardiomyopathy

- "Selected first-degree relatives refers to relatives who are willing to undergo further testing and who could benefit from further screening and testing (and not the terminally ill patients or those who do not want to be screened and tested)."
- "Arrhythmogenic right ventricular cardiomyopathy is detected clinically in approximately 35% to 40% of first-degree relatives, most commonly in siblings or symptomatic first-degree relatives"
- "The proband with arrhythmogenic right ventricular cardiomyopathy is usually diagnosed by the presence of clinical symptoms along with the presence of arrhythmogenic right ventricular cardiomyopathy Task Force criteria"
- "A pathogenic genetic mutation was added to the major Task Force criteria in 2010. The yield of genetic testing in probands with suspected arrhythmogenic right ventricular cardiomyopathy is generally 30% to 54%, and is up to 58% among patients with a strong family history of SCD in multiple members. A negative genetic test for arrhythmogenic right ventricular cardiomyopathy does not exclude the disease, and a positive genetic test currently does not guide therapy."

Hypertrophic Cardiomyopathy

- "In first-degree relatives of patients with HCM due to a known causative mutation, genetic counseling and mutation-specific genetic testing are recommended."
- "In patients with clinically suspected or diagnosed HCM, genetic counseling and genetic testing are reasonable."

Cardiac Channelopathies

- In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT

syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended (I)

- Clinical screening of first-degree relatives of patients with inherited arrhythmia syndromes is crucial to identifying affected family members. Due to the increased risk of adverse cardiac events in genotype positive patients with long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, targeted screening for the identified family-specific mutation can identify individuals who are at risk for these adverse outcomes

Congenital Long QT Syndrome

- In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended (I)
- Genetic testing for disease-causing mutations in long QT syndrome offers important diagnostic, prognostic, and therapeutic information in addition to the clinical evaluation, and a positive test can facilitate establishing risk for family members. The yield of genetic testing in long QT syndrome phenotype-positive patients is 50% to 86%, with the higher range present in patients with marked QT prolongation or positive family history of SCD. A negative genetic test does not exclude the diagnosis of long QT syndrome, which relies on the clinical evaluation.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable (IIa)
- Genetic testing may be useful to confirm the diagnosis of catecholaminergic polymorphic ventricular tachycardia, which is suggested by the development of bidirectional VT with exertion or stress. Recognition of catecholaminergic polymorphic ventricular tachycardia as the cause for exertional symptoms should prompt aggressive therapy to prevent the significant risk of SCD. Therapy for catecholaminergic polymorphic ventricular tachycardia is not guided by genotype status, but screening of first-degree relatives may be facilitated with genetic testing.

Brugada Syndrome

- In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives (IIb)
- The yield of genetic testing in phenotype positive patients is approximately 20% to 30% in Brugada syndrome. SCN5A variants account for most of this subset of genotype positive Brugada syndrome. However, 2% to 10% of otherwise healthy individuals host a rare variant of SCN5A. A negative genetic test does not exclude the diagnosis of Brugada syndrome, which is usually based on electrocardiographic and clinical characteristics. Risk stratification is based on symptoms and clinical findings; genotype status is not correlated with the risk of adverse events. Identification of a pathogenetic mutation may help facilitate

recognition of carrier status in family members, allowing for lifestyle modification and potential treatment.

Short QT syndrome

- In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives (IIb)
- Pathogenic mutations in potassium channels have been identified in approximately 10% to 20% of patients with short QT syndrome, including in KCNH2 (SQT1), KCNQ1 (SQT2), and KCNJ2 (SQT3).

Early Repolarization "J-wave" Syndrome

- In patients with early repolarization pattern on ECG, genetic testing is not recommended (III-no benefit)

Postmortem Evaluation of SCD

- In first-degree relatives of SCD victims who were 40 years of age or younger, cardiac evaluation is recommended, with genetic counseling and genetic testing performed as indicated by clinical findings (I)
- For the purpose of family risk profiling, it is important to use the disease-specific genetic test panel that corresponds to the autopsy findings. Risk profiling of family members of an SCD victim suspected of having an inherited cardiomyopathy at autopsy is important. Although phenotyping of surviving family members is crucial, genotyping of the SCD proband provides a mechanism for efficient follow-up evaluation of those relatives with the disease-causing mutation found in the proband (Al-Khatib Sana et al., 2018).

American College of Medical Genetics and Genomics (ACMG, 2016)

The American College of Medical Genetics and Genomics (ACMG) included several myopathies and channelopathies in their "minimum" list of genes for which mutations should be reported when whole genome sequencing is performed for other primary purposes (incidental findings). Those genes are listed below:

- RYR2 for Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- KCNQ1, KCNH2, SCN5A for Romano-Ward Long QT syndromes and Brugada syndrome
- MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, and LMNA for DCM and HCM
- PKP2, DSP, DSC2, TMEM43, and DSG2 for ARVC (Kalia et al., 2016)

Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA) Expert Consensus Statement (2011, reaffirmed 2018)

Hypertrophic Cardiomyopathy (HCM)

Class I recommendations (is recommended):

- "Comprehensive or targeted (MYBPC3, MYH7, TNNI3, TNNT2, TPM1) 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 genetic testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case."

Dilated Cardiomyopathy (DCM)

Class I recommendations:

- "Comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (i.e., first-, second-, or third- degree heart block) and/or with a family history of premature unexpected sudden death."
- "Mutation-specific testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case."

Class IIa recommendations:

- Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Class I recommendations:

- "Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the ACM/ARVC- causative mutation in an index case."

Class II recommendations:

- "Comprehensive or targeted (DSC2, DSG2, DSP, JUP, PKP2, and TMEM43) ACM/ARVC genetic testing can be useful for patients satisfying task force diagnostic criteria for ACM/ARVC." (II-A, can be useful)
- "Genetic testing may be considered for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 task force criteria (European Heart Journal)." (II-B, may be considered)

Left Ventricular Noncompaction (LVNC)

Class I recommendations:

- "Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a LVNC-causative mutation in the index case."

Class II recommendations:

- LVNC genetic testing can be useful for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype. (II-A)

Restrictive Cardiomyopathy (RCM)

Class I recommendations:

- "Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a RCM-causative mutation in the index case."

Class II recommendations:

- "RCM genetic testing may be considered for patients in whom a cardiologist has established a clinical index of suspicion for RCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype." (II-B)

Long-QT Syndrome

Class I recommendations:

- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype OR for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults).
- Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

Class II recommendations:

- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs. (II-B)

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Class I recommendations:

- Comprehensive or CPVT1 and CVPT2 (RYR2 and CASQ2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion.
- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.

Brugada Syndrome

Class I recommendations:

- Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

Class II recommendations:

- Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype (II-A)

Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

Short QT syndrome

Class I recommendations:

- 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 II recommendations:

- 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.

Sinus Node Dysfunction (SND)

- "In idiopathic sinus node dysfunction (SND), mutations in the cardiac pacemaker channel gene *HCN4* and in sodium channel genes can be identified in an unknown portion. However, because non-genetic causes appear more frequently in idiopathic SND, genetic testing for idiopathic SND should be considered on an individual basis (M.J. Ackerman et al., 2011)."

Progressive Cardiac Conduction Disease (CCD)

- "Genetic testing may be considered as part of the diagnostic evaluation for patients with either isolated CCD or CCD with concomitant congenital heart disease, especially when there is documentation of a positive family history of CCD."
- "Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CCD-causative mutation in an index case."
- "Taken together, tiered genetic testing for patients with CCD and congenital heart disease or cardiomyopathies is useful because other cardiac and non-cardiac disease features may be present or may develop; individual genes should be considered after discussion of clinical features with an experienced cardiogenetic center (M.J. Ackerman et al., 2011)."

Post-Mortem Genetic Testing in Sudden Unexpected Death Cases

- "In the setting of autopsy-negative SUDS, comprehensive or targeted (*RYR2, KCNQ1, KCNH2*, and *SCN5A*) ion channel genetic testing **may be considered** in an attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives and **is recommended** if circumstantial evidence points toward a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death)."
- "Mutation-specific genetic testing is recommended for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent" (M.J. Ackerman et al., 2011).

Canadian Cardiovascular Society/Canadian Heart Rhythm Society (2011)

Long QT Syndrome

Genetic testing is recommended in the cardiac arrest survivor with LQTS for the primary purpose of screening first-degree relatives, in the patient with syncope and QTc prolongation that is attributed to LQTS, and in the asymptomatic patient with consistent QTc prolongation that is clinically suspected to represent LQTS.

Brugada Syndrome

Genetic testing in the cardiac arrest survivor, patient with syncope, or asymptomatic patient with a persistent or provocable type 1 Brugada ECG pattern is recommended for the primary purpose of

screening of family members. However, patients with types 2 or 3 Brugada ECG patterns are not recommended for genetic testing.

CPVT

Genetic testing is recommended for the primary purpose of screening family members (Gollob et al., 2011).

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

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

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

European Society of Cardiology (ECS, 2014)

Genetic counselling is recommended for all HCM patients when the HCM is not explained solely by a non-genetic cause.

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

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

The Heart Failure Society of America (HFSA)/The American College of Medical Genetics and Genomics (ACMG)

The HFSA/ACMG published a practice guideline in 2018 on the Genetic Evaluation of Cardiomyopathy. The following recommendations for genetic testing for cardiomyopathies were made (Hershberger et al., 2018):

Recommendation 1. Genetic testing is recommended for all patients with cardiomyopathy

- Genetic testing is recommended for the most clearly affected family member.
- Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
- In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended and genetic testing should be considered.

Core genes associated:

Type	Genes	Estimated Yield Diagnostic Testing
HCM	MYH7, MYBPC3, TNNT2, TNNC1, TNNI3, TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKG2, LAMP2, GLA	30-60%
DCM	TTN, LMNA, MYH7, TNNT2, BAG3, RBM20, TNNC1, TNNI3, TPM1, SCN5A, PLN, plus all HCM and ARVC genes	10-40%

ARVC	DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, PLN, RYR2, SCN5A, TMEM43, TTN, consider full DCM panel	10-50%
RCM	Consider HCM or DCM gene panel	10–60%
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Unknown

The specific cardiomyopathy comments are as follows:

HCM

- "Beyond sarcomeric genes, core genes to screen in patients with HCM include GLA, PRKAG2, and LAMP2."
- "Consultation with a geneticist is indicated."

DCM

- "Core genes to be tested in individuals with DCM include genes encoding sarcomeric and cytoskeletal proteins."
- "Genetic testing is important in mothers of individuals with Duchenne or Becker to determine carrier status because carrier females may develop DCM in the third to fifth decade of life."

LVNC

"Genetic testing is not recommended when the LVNC phenotype is identified serendipitously in asymptomatic individuals with otherwise normal cardiovascular structure and function."

American College of Cardiology Foundation/American Heart Association

The 2013 ACCF/AHA Guideline for the Management of Heart Failure states that: "Increasingly, it is recognized that many (20% to 35%) patients with an idiopathic DCM have a familial cardiomyopathy (defined as 2 closely related family members who meet the criteria for idiopathic DCM)." "Advances in technology permitting high-throughput sequencing and genotyping at reduced costs have brought genetic screening to the clinical arena" and refers to the 2009 and 2011 published guidelines. The guidelines further note that genetic testing may be considered in conjunction with counseling in familial DCM (Yancy et al., 2013).

Heart Rhythm Society (HRS, 2019)

Arrhythmogenic Cardiomyopathies

The HRS published an "Expert Consensus Statement" on "Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy". In it, they include recommendations on genetic testing for this set of cardiac disorders.

"For individuals and decedents with either a clinical or necropsy diagnosis of ACM, genetic testing of the established ACM-susceptibility genes is recommended."

"For genetic testing of the established ACM-susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended."

"When a likely pathogenic or pathogenic genetic variant has been identified in the proband, cascade genetic testing can be offered to first-degree at-risk relatives… Cascade genetic testing is therefore only offered to family members where a likely pathogenic or pathogenic variant in a known disease-associated gene is identified in the proband…" (Towbin et al., 2019).

American Heart Association

The AHA published a guideline regarding cardiomyopathy in children. In it, they state that "genetic testing should first be performed in the individual known to have a specific cardiomyopathy phenotype and should be informed by the child's overall presentation, with a detailed examination looking for dysmorphic features, muscle weakness, scoliosis, or specific laboratory findings." They also state that indications for genetic testing include "determining the cause of HCM, predicting the clinical course and severity, screening first-degree relatives, and determining recurrence risk".

This guideline addresses HCM, DCM, RCM, LVNC, Arrhythmogenic Ventricular Cardiomyopathy (both right and left ventricles), as well as cardiomyopathy caused by channelopathies such as Long-QT syndrome (Lipshultz Steven et al., 2019).

The AHA also published a guideline discussing early repolarization. In it, they remark that the biological basis for early repolarization pattern "remains incompletely understood". Therefore, the AHA proposes "large-scale, unbiased (eg, genome-wide association studies), family-guided genetic discovery approaches, as well as efforts aimed at understanding both the mechanisms underlying ER and the associated arrhythmogenesis" (Patton Kristen et al., 2016).

Applicable Federal Regulations

Searches on the FDA website for "channelopathy" or "cardiomyopathy" yielded no relevant results on March 6, 2020 (FDA, 2020). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

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

Applicable service codes: 81401, 81403, 81404, 81405, 81406, 81407, 81408, 81413, 81414, 81439, 81479, 96040, S0265, S3861 S3865, S3866

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

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Policy Implementation/Update Information

For policy titled: Genetic Testing for Cardiac Ion Channelopathies:

1/1/2019 BCBSNC will provide coverage for genetic testing for cardiac ion channelopathies when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

For policy titled: Genetic Testing for Inherited Cardiomyopathies and Channelopathies:

10/1/2019 Reviewed by Avalon 2nd Quarter 2019 CAB. Policy extensively revised to include description and guidelines for cardiomyopathies. Policy statement revised to include "cardiomyopathies" and as follows: to the When Covered section added items #8-14; When Not Covered section added 2 additional "not medically necessary" statements and 1 "investigational" statement regarding HCM; Added the following to the 2nd to last statement regarding Genetic testing for Early Repolarization "J-wave" Syndrome, Sinus Node Dysfunction (SND) and/or other rhythm disorders is considered investigational. Related Policies added to Description section. References updated. Medical Director review 9/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

4/28/20 Specialty Matched Consultant Advisory Panel review 4/2020. Medical Director review 4/2020. (jd)

7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Policy guidelines and references updated. The following codes were added to the Billing/Coding section: S3865, S3866. Medical Director review 7/2020. (jd)