

Cardiac Channelopathies

Disease States Overview

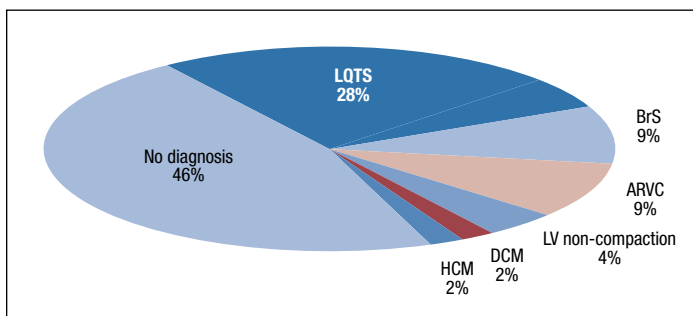
According to the Centers for Disease Control and Prevention, each year in the United States more than 600,000 people die from heart disease. Approximately 22,000 of those deaths occur in young, seemingly healthy people ≤ 44 years of age. Over 50% of sudden arrhythmic deaths are caused by inherited cardiac syndromes (Figure 1).¹ Some common causes of sudden cardiac death include: Long QT Syndrome (LQTS), Brugada Syndrome (BrS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Short QT Syndrome (SQTS), Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Conduction Disease associated with DCM (CD-DCM) and Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC).

About Long QT Syndrome

LQTS is three times more common than childhood leukemia.² While the symptoms associated with LQTS commonly present during childhood and adolescence, the risk of initial and repeat cardiac events persists into adulthood (including ≥ 40 years of age).^{3,4} Greater awareness of and improved testing for LQTS is revealing the disease's true prevalence; it is now estimated that 1 in 2,500 people has LQTS (Figure 2).⁵

LQTS symptoms include heart palpitations, syncope, seizure and/or sudden cardiac death. These symptoms are often in response to a specific trigger such as exercise or emotional stress. ECG results may reveal prolonged ventricular repolarization (QT-interval prolongation), and death may occur secondary to a stereotypical arrhythmia called torsades de pointes.

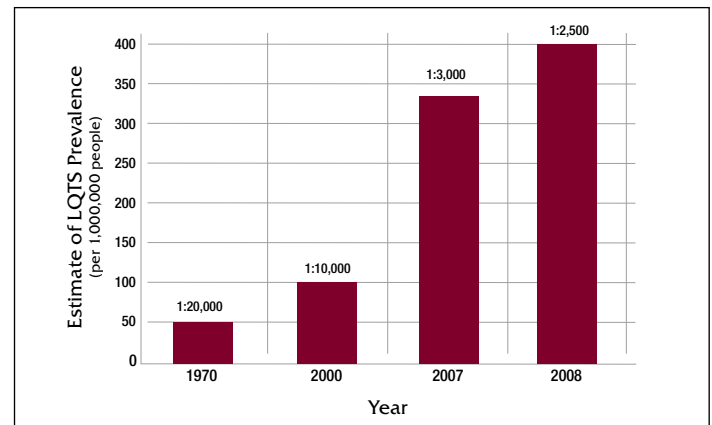
Figure 1: Inherited Diseases that Cause Sudden Arrhythmic Death



Adapted from: Behr ER, et al. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in majority of families. *Eur Heart J.* 2008;29:1670-1680.

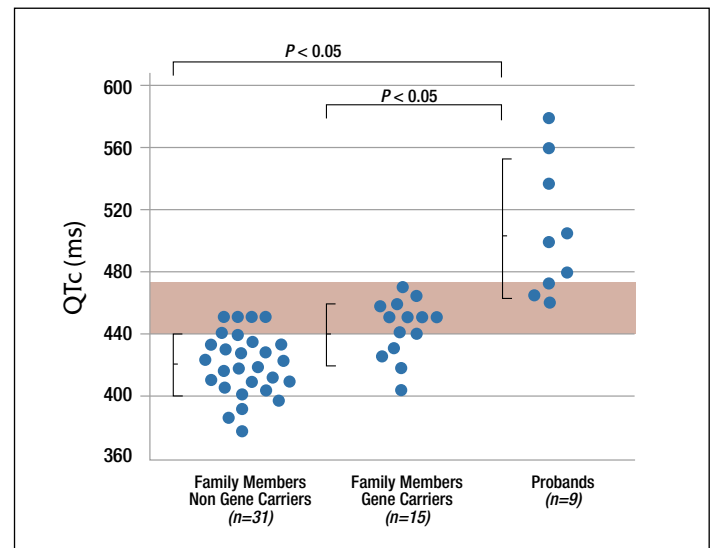
Most at-risk family members do not present with the typical LQTS phenotype and therefore require genetic testing to confirm the presence or absence of disease (Figure 3).⁶ This is one of the reasons that the ACC/AHA/ESC guidelines (2006), advocate that ALL mutation carriers in an LQTS family should undergo genetic screening. (Figure 3).⁶

Figure 2: True Prevalence of LQTS



Adapted from: Crotti L, et al. Congenital long QT syndrome. *Orphanet Journal of Rare Diseases.* 2008;3:18.

Figure 3: LQTS QTc Variability Within Families



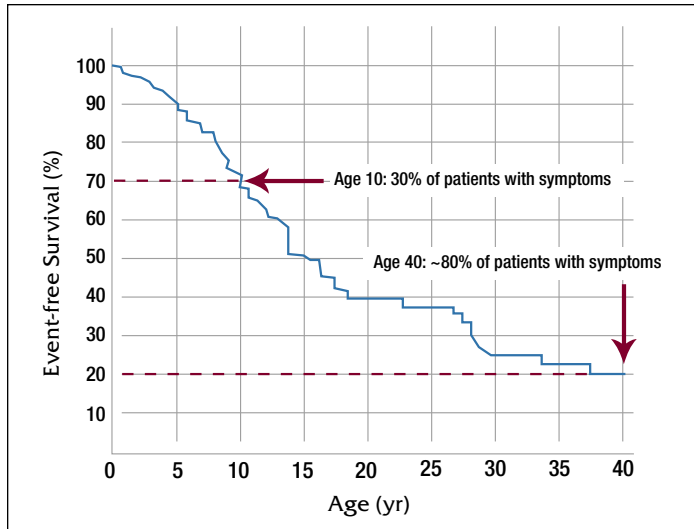
Adapted from: Priori SG, et al. Low penetrance in the long-QT syndrome: clinical impact. *Circulation.* 1999;99:529-533.

About CPVT

CPVT is considered the most lethal of the channelopathies. If untreated, 80% of CPVT patients will develop symptoms by age 40 (Figure 4).⁷ The overall mortality of untreated CPVT patients is 30-50%.⁸ Cardiac events associated with CPVT are triggered by physical and/or emotional stress. Select symptoms include heart palpitations, syncope and sudden cardiac death.

A resting ECG will not reveal CPVT. Even when exercise stress testing is done, the characteristic ECG tracing may not be elicited.^{7,8}

Figure 4: Cardiac Event-free Survival for CPVT Patients



Adapted from: Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:675-678.

About Brugada Syndrome

The exact prevalence of BrS is unknown.⁹ The most common presentation is a male in his 40s with malignant arrhythmias and a history of syncope.⁹ Males with an abnormal ECG and inducible ventricular arrhythmias have a poor prognosis.⁹ If untreated, the mean age of death is approximately 40 years. If left untreated, men with BrS have a 45% chance of having a cardiac during their lifetime.⁹

About Short QT Syndrome

SQTS was discovered in the year 2000. The exact prevalence is unknown, however it is estimated that approximately 30 people have been diagnosed with SQTS since its discovery. Symptoms include palpitations, syncope and sudden cardiac death. There is no clear QT interval value for diagnosing SQTS; however a QT interval that consistently measures ≤ 360 msec is suggestive.

Challenges Associated With Diagnosing LQTS

Making a clinical diagnosis of LQTS can be challenging. Some of the most common challenges include:

1. Disease Variability

- LQTS is a heterogeneous disease with significant phenotypic variability, even among members of the same family.
- The penetrance of LQTS is variable; as many as 33% of LQTS carriers will never have a symptom.⁶

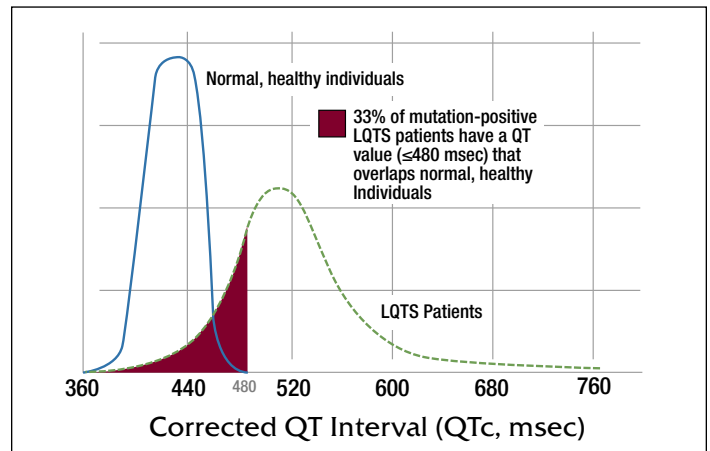
2. ECG Variability

- Approximately 33% of mutation-positive LQTS patients have a QT interval (≤ 480 msec) that overlaps normal, healthy individuals (Figure 5).¹⁰
- Several factors may influence an ECG, including:¹¹
 - Genetics
 - Age and gender
 - CNS disorders
 - Electrolyte alterations
 - Certain medications

3. Signs and Symptoms Do Not Differentiate LQTS Subtypes

- Differentiating LQTS subtype is important to risk stratification and developing an effective treatment plan.

Figure 5: Overlap of LQTS Patients With Normal, Healthy Individuals



Adapted from: Taggart NW, et al. Diagnostic miscues in congenital long-QT syndrome. *Circulation*. 2007;115:2613-2620.

Challenges Associated With Diagnosing CPVT

1. CPVT Cannot be Diagnosed with a Resting ECG.
 - It is estimated that 30% of CPVT patients have been misdiagnosed as “Long QT with a normal QT interval.”⁷
2. CPVT Cannot be Differentiated From LQTS Based Upon Symptom Triggers
 - Failure to distinguish CPVT from LQTS can influence treatment selection. Beta-blockers do not provide adequate protection for CPVT patients. Nearly 50% of CPVT patients taking a beta-blocker continue to experience symptoms.⁷

Challenges Associated With Diagnosing BrS

1. The ECG Abnormalities Associated with BrS May Not be Evident Until Unmasked by Infusion of a Sodium Channel Blocker (Flecainide or Procainamide).⁹
2. May Get False-positives Due to Drug induced ECG Abnormalities.

Challenges Associated With Diagnosing SQTS

1. SQTS is Extremely Rare.
2. Diagnostic Criteria not Available and the Lower Limit of the QT Interval has not Been Fully Established.
3. The QT Interval Will Often be Normal During Tachycardia and Show no or Minimal Prolongation With a Decrease in Heart Rate.

The Role of the *FAMILION* Family of Genetic Tests for Cardiac Channelopathies

The *FAMILION* family of genetic tests for channelopathies detects genetic variants associated with LQTS, CPVT, SQTS and BrS.

By reducing uncertainty and finding the specific causes of these cardiac channelopathies, genetic testing provides the following clinical benefits:

- Aids in the diagnosis or confirmation of diagnosis
- Aids in comprehensive risk assessment
- Guides lifestyle modifications
- Provides information needed to develop a comprehensive treatment plan, which may include the placement of an internal cardioverter defibrillator (ICD)
- Identifies presymptomatic mutation carriers
- Helps establish the need and schedule for clinical surveillance of family members
- Better enables genetic counseling

The Expected Yield for the *FAMILION* LQTS, BrS, CPVT and SQTS Tests

The *FAMILION* LQTS Test includes 11 LQTS causative genes and will identify a mutation in 75-80% of patients with a high index of suspicion for LQTS.^{12,13}

The *FAMILION* Brugada Syndrome Test includes 7 BrS causative genes and will identify a mutation in 25-40% of patients with a high index of suspicion for Brugada Syndrome.^{9,14,15,16,17,18,19,20}

The *FAMILION* CPVT Test includes 2 CPVT causative genes and will identify a mutation in 65-75% of patients with a high index of suspicion for CPVT.^{7,21,22,23}

- 60-65% of CPVT is caused by mutations in the *RYR2* gene.^{7,21}
- 5-10% of patients diagnosed with CPVT have a mutation in the *KCNJ2* gene.^{22,23}

The yield associated with the *FAMILION* SQTS Test is unknown.

Figure 6: The *FAMILION* LQTS, BrS, CPVT and SQTS Tests

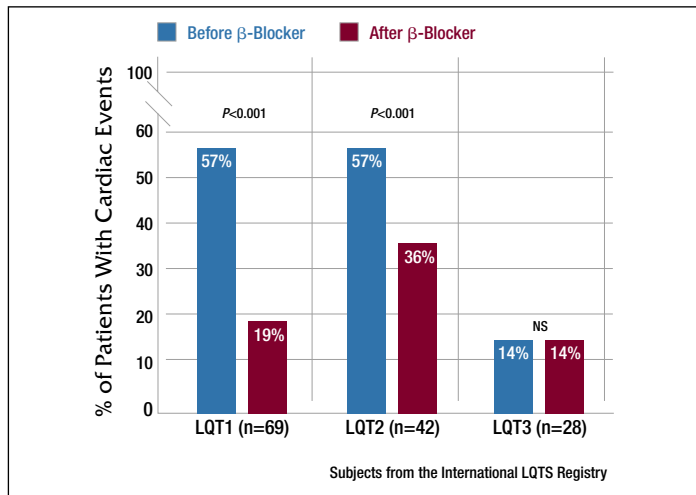
Cardiac Channelopathies	Genes*			
LQTS Test	<i>KCNQ1</i> (LQT1) <i>KCNE2</i> (LQT6) <i>SCN4B</i> (LQT10)	<i>KCNH2</i> (LQT2) <i>KCNJ2</i> (LQT7) <i>AKAP9</i> (LQT11)	<i>SCN5A</i> (LQT3) <i>CACNA1C</i> (LQT8) <i>SNTA1</i> (LQT12)	<i>KCNE1</i> (LQT5) <i>CAV3</i> (LQT9)
BrS Test	<i>SCN5A</i> <i>CACNB2</i>	<i>GPD1L</i> <i>SCN1B</i>	<i>CACNA1C</i> <i>KCNE3</i>	<i>SCN3B</i>
CPVT Test	<i>RYR2</i>	<i>KCNJ2</i>		
SQTS Test	<i>KCNH2</i>	<i>KCNQ1</i>	<i>KCNJ2</i>	

* See the *FAMILION* technical specification sheet for coverage areas.

The Impact of the *FAMILION* LQTS Test on Clinical Decisions

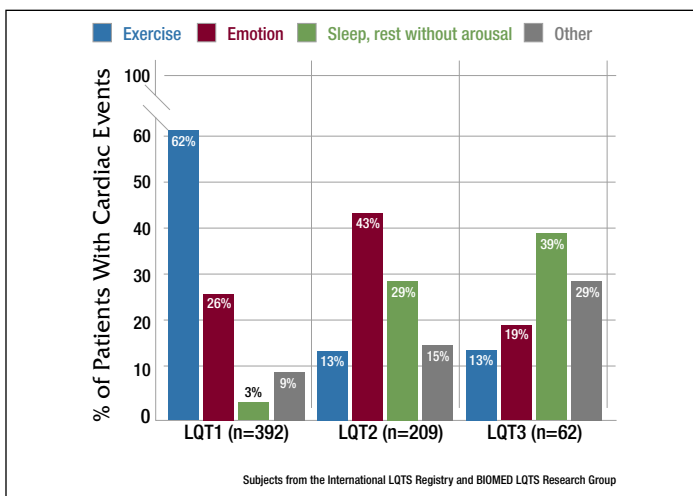
The *FAMILION* LQTS Test provides important information that helps guide pharmacologic and non-pharmacologic treatment decisions.^{24,25} LQTS is divided into several subtypes based on the mutation found. Multiple studies have identified distinct characteristics that differentiate the three most common LQTS genetic subtypes (LQT1, LQT2 and LQT3). For instance, the effectiveness of beta-blocker therapy has been shown to differ significantly by LQTS subtype (Figure 7).²⁴ Knowing this information may help in developing a more effective treatment plan.²⁴

Figure 7: Efficacy of Beta-blocker Therapy for Patients With a Known LQTS Genotype



Adapted from: Moss AJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation*. 2000;101:616-623.

Figure 8: Arrhythmic Triggers by LQTS Subtype



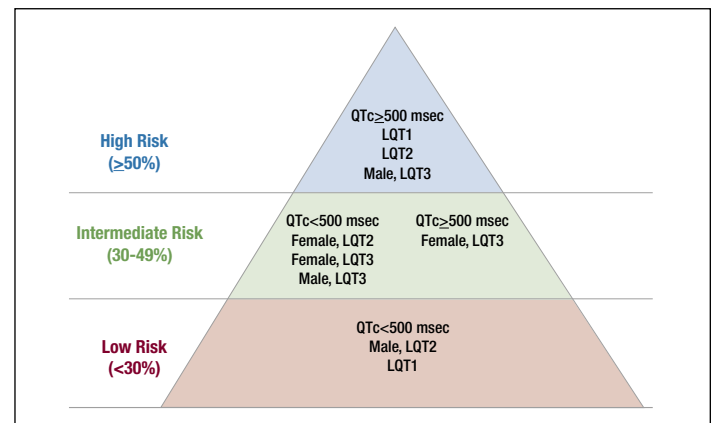
Adapted from: Schwartz PJ, et al. Genotype-phenotype correlation in the long-QT syndrome: gene specific triggers for life-threatening arrhythmias. *Circulation*. 2001;103:89-95.

Additionally, triggers associated with cardiac events are correlated with LQTS subtype (Figure 8).²⁵ Knowing a patient's LQTS subtype can help guide choice of therapeutic intervention lifestyle modifications, thereby reducing the probability of cardiac events.²⁵

LQTS Subtype and Mutation Location Help Define Risk—The *FAMILION* LQTS Test Provides Both

Knowing LQTS subtype is important to risk stratification. The risk-stratification scheme in Figure 9 shows the probability of a first cardiac event before the age of 40 in the absence of treatment. This algorithm uses LQTS subtype, QTc and patient gender to better assign risk.²⁶

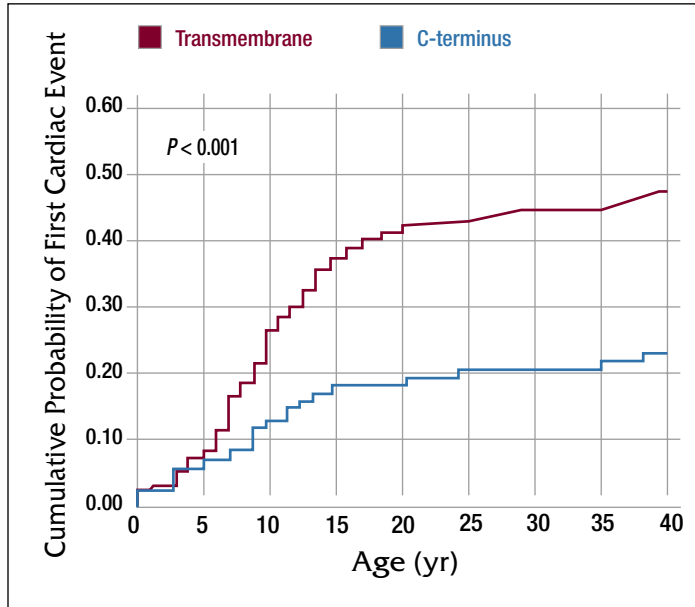
Figure 9: Published Scheme for Risk Stratification Among Patients With Long QT Syndrome According to Genotype, Gender and QTc



Adapted from: Priori SG, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348(19):1866-1874.

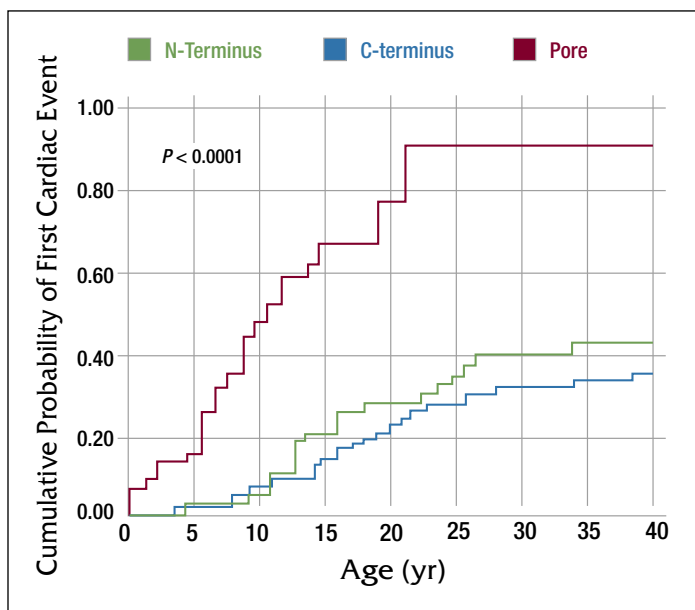
For LQTS patients, the risk of having a cardiac event is strongly correlated to genetic subtype and the location of the gene mutation. Multiple studies support the association between pathogenic disease and mutation location (Figures 10 and 11).^{27,28}

Figure 10: LQT1 Mutations in the Transmembrane Region Carry Greater Risk



Adapted from: Moss AJ, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation*. 2007;115:2481-2489.

Figure 11: LQT2 Mutations in the Pore Region Carry Greater Risk



Adapted from: Moss AJ, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation*. 2002;105:794-799.

The ACC/AHA/ESC Guidelines (2006) Support Genetic Testing for the Identification of ALL Mutation Carriers in a Channelopathy Family

The ACC/AHA/ESC guidelines for management of patients with ventricular arrhythmias and prevention of sudden cardiac death recommends genetic testing for LQTS, CPVT and BrS.

Long QT Syndrome

“Genetic analysis is very important for identifying all mutation carriers within an LQTS family; once identified, silent carriers of LQTS genetic defects may be treated with beta-blockers for prophylaxis of life-threatening arrhythmias. Furthermore, silent mutation carriers should receive genetic counseling to learn about the risk of transmitting LQTS to offspring.”²⁹

“In patients affected by LQTS, genetic analysis is useful for risk stratification and for making therapeutic decisions.”²⁹

CPVT

“Genetic analysis may help identify silent carriers of catecholaminergic VT-related mutations; once identified, silent carriers may be treated with beta-blockers to reduce the risk of cardiac events and may receive appropriate genetic counseling to assess the risk of transmitting the disease to offspring.”²⁹

Brugada Syndrome

“Genetic analysis may help identify silent carriers of Brugada syndrome-related mutations so that they can remain under clinical monitoring to detect early manifestations of the syndrome. Furthermore, once identified, silent mutation carriers should receive genetic counseling and discuss the risk of transmitting the disease to offspring.”²⁹

The Cost Effectiveness of the FAMILION LQTS Test

The cost-effectiveness of the FAMILION LQTS Test has been evaluated. FAMILION was found to be a cost-effective tool to aid in the diagnosis and treatment of LQTS.³⁰ The authors concluded:

“A genetic test for familial LQTS is cost effective relative to no testing, given our assumptions about the population to be tested and the relevant probabilities and costs. The primary benefit of testing is to more accurately diagnose and treat individuals based on a combination of clinical scores and test results.”³⁰

“We found that genetic testing is more cost effective than not testing at a cost per year of life saved of \$2,500. The cost per year of life saved is well below the standard threshold of \$50,000 per life-year saved, which often is used to define a cost-effective intervention.”³⁰

PGxHealth Laboratory Process Highlights

For all regions sequenced, direct sequencing is performed in forward and reverse directions. In select instances a sequencing constraint may exist, these regions are amplified twice and sequenced in a single direction.

The following laboratory processes are among the reasons PGxHealth is a leader in genetic testing:

- Two technologists independently score all sequence variants, and a supervisor reconciles any discrepancy.
- All traces with variants are reviewed and approved by an American Board of Medical Genetics board-certified molecular geneticist.
- For each class I or II mutation found, a second round of PCR amplification and sequencing are completed to confirm the initial finding.
- Identified variants are interpreted with respect to an ethnically diverse reference population of several hundred unrelated individuals (presumed non-channelopathy), a database of known mutations and published medical literature (Figure 12).

Figure 12: The *FAMILION* Test Variant Classification

Class I Mutation: Deleterious and Probable Deleterious Mutations
Class II Mutation: Variant of Uncertain Significance
Class III Variant: Variant Not Generally Expected to Cause Disease
Class IV Variant: Non-protein-altering Variant

PGxHealth Reimbursement Highlights

- PGxHealth is an approved Medicare provider.
- PGxHealth is an approved Medicaid provider in most states. PGxHealth reserves the right not to participate in any state's Medicaid program even if approved as a provider.
- A brief list of select insurance companies that have developed positive medical policies for all or select *FAMILION* tests include: BCBSA, United, Aetna, Cigna and Humana.

Every Test Report is Accompanied by an Interpretation Guide

- All test reports include a test-specific interpretation guide. These were developed to better explain the system employed by PGxHealth for rating variants (Figure 13).

Figure 13: The *FAMILION* Tests Interpretation Guide

	← Related to Disease	Not Related to Disease →	
	Class I Mutation (Deleterious or Probable Deleterious)	Class II Mutation (Variant of Uncertain Significance)	Class III Variants (Not Expected to Cause Disease)
Clinical Interpretation	<ul style="list-style-type: none"> • Result strongly suggests an inherited cardiac disease. 	<ul style="list-style-type: none"> • Mutation may be disease-causing or benign. 	<ul style="list-style-type: none"> • Class III variants are not expected to be disease-causing. A report with only Class III variants is considered negative.
Reasons for Classification	<ul style="list-style-type: none"> • Strong evidence of deleteriousness. • “Probable,” if included, indicates that variant is predicted, but has not been demonstrated, to cause disease. • Typically absent from a healthy control population. 	<ul style="list-style-type: none"> • Evidence is insufficient to determine whether the mutation is deleterious. • Typically absent from a healthy control population. 	<ul style="list-style-type: none"> • Evidence indicates variant is not disease-causing. • Typically common in a healthy control population.
Recommendations	<ul style="list-style-type: none"> • Genetic testing of all first-degree relatives is recommended to identify those at risk for disease. Genetic counseling should be considered. 	<ul style="list-style-type: none"> • Genetic testing and clinical screening in family members may elucidate the significance of the mutation. Genetic counseling should be considered. 	<ul style="list-style-type: none"> • Genetic testing of family members for Class III variants is not advised.

The FAMILION Family of Genetic Tests

Cardiac Channelopathies	Genes*				Clinical Sensitivity†
LQTS Test	KCNQ1 (LQT1) KCNE2 (LQT6) SCN4B (LQT10)	KCNH2 (LQT2) KCNE3 (LQT7) AKAP9 (LQT11)	SCN5A (LQT3) CACNA1C (LQT8) SNTA1 (LQT12)	KCNE1 (LQT5) CAV3 (LQT9)	75-80% ^{1,2}
BrS Test	SCN5A SCN1B	GPD1L KCNE3	CACNA1C SCN3B	CACNB2	25-40% ^{3,4,5,6,7,8,9}
CPVT Test	RYR2	KCNJ2			65-75% ^{10,11,12,13}
SQTS Test	KCNH2	KCNQ1	KCNJ2		Unknown
Cardiomyopathies	Genes*				Clinical Sensitivity†
ARVC Test	DSP PKP2	DSG2 DSC2	TMEM43		40-50% ¹⁴
DCM Test	LMNA ANKRD1 TNNC1	SCN5A TPM1 MYBPC3	ACTC LDB3 PLN	MYH7 TNNT2 TNNI3	~25% ^{2,15}
CD-DCM Test	LMNA	SCN5A			40-50% ^{16,17}
HCM Test	MYH7 TPM1 MYBPC3	TNNC1 TNNT2 TNNI3	ACTC MYL2 MYL3	GLA LAMP2 PRKAG2	50-60% ¹⁸

* See the FAMILION test specification sheet for coverage areas. † Percent of patients with a high index of suspicion for the cardiac syndrome that will have a mutation identified.

FAMILION Tests Table References:

1. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. *Heart Rhythm*. 2005;2:507-517. 2. Data on File, PGxHealth. Multiple studies available upon request. 3. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm*. 2010;7:33-46. 4. London B, Michalec M, Mehdi H, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation*. 2007;116:2260-8. 5. Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation*. 2007;115:442-9. 6. Antzelevitch C, Nof E, et al. Brugada syndrome: recent advances and controversies. *Curr Cardiol Rep*. 2008;10:376-83. 7. Watanabe H, Koopmann TT, Le Scouarnec S, et al. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest*. 2008;118:2260-8. 8. Delpón E, Cordeiro JM, Núñez L, et al. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythm Electrophysiol*. 2008;1:209-18. 9. Hu D, Barajas-Martinez H, Burashnikov E, et al. A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circ Cardiovasc Genet*. 2009;2:270-8. 10. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2009;119:2426-34. 11. Medeiros-Domingo A, Tester DJ, Makielski JC, et al. Spectrum of mutations in RYR2, CASQ2 and KCNJ2 genes and genotype-phenotype correlation in a cohort of unrelated cases referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. *Heart Rhythm Society 2009 Scientific Sessions. Heart Rhythm*. 2009;6:S102. 12. Ruan Y, Theilade J, Memmi M, et al. KCNJ2 mutations in patients referred for catecholaminergic polymorphic ventricular tachycardia gene screening. *American Heart Association 2007 Scientific Sessions. Circulation*. 2007;116:492. 13. Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:675-678. 14. Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2007;50:1813-1821. 15. Hershberger RE, Kushner JD, Parks SB. Dilated Cardiomyopathy Overview. In: *GeneReviews at GeneTests: Medical Genetics Information Resource*. University of Washington, Seattle. 1997-2009. Available at <http://www.genetests.org>. Accessed 10/14/2009. 16. Fatkin D, et al. *NEJM*. 1999;341:1715-24. 17. Hershberger RE, et al. *Journal of Cardiac Failure*. 2009;15:83-97. 18. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. *Nat Clin Pract Cardiovasc Med*. 2008;5:158-168.

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Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:675-678. 8. Mohamed U, Napolitano C, Priori SG. Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol*. 2007;18(7):791-797. 9. Brugada R, Brugada P, Brugada J, Hong K. Brugada syndrome. *Gene Reviews Web site*. Available at: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=brugada>. Accessed May 25, 2009. 10. Taggart NW, Haglund CM, Tester DJ, Ackerman MJ. Diagnostic miscues in congenital long-QT syndrome. *Circulation*. 2007;115:2613-2620. 11. Maron BJ, Moller JH, Seidman CE, et al. Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular diseases: hypertrophic cardiomyopathy, long-QT syndrome, and marfan syndrome. *Circulation*. 1998;98(14):1460-1471. 12. Tester DJ, Will ML, Haglund CM, Ackerman MJ. 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